Chronic hypertension in pregnancy

Evaluating mechanism and treatment in an ethnically diverse group to assess factors contributing to maternal and perinatal outcome

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Chronic hypertension in pregnancy: evaluating mechanism and treatment in an ethnically diverse group to assess factors contributing to maternal and perinatal outcome

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STATEMENT OF OWN WORK

I wrote the protocol and conducted the systematic review (Chapter 3) with Dr Fran Conti-Ramsden as second reader. Mr Paul Seed and I completed the statistical analysis together. I wrote the first draft of the manuscript and edited in response to co-authors' comments. It is presented in the final submitted format for publication. The cohort study (Chapter 4) built on audit data initially collected at St Thomas' Hospital. I added to this dataset, incorporating data provided by Professor Basky Thilaganathan (St George's Hospital) and Dr Jenny Myers (Manchester). I cleaned the data, calculated GROW birthweight centiles for the cohort then undertook statistical analysis with Mr Paul Seed. I wrote the first draft of the manuscript, edited in response to co-authors' comments and am currently submitting it for publication.

I have been directly involved with the PANDA study since the inception of the research question based on research recommendations from the NICE Hypertension in Pregnancy guideline. I wrote the first draft of all three grant applications, designed the protocol and other study specific literature (patient information sheets and consent forms), and was involved in applying to the MHRA and REC for the necessary approvals. As Trial Co-ordinator, I was directly involved with setting the study up at the four sites, enrolling and following women up in the study, and collecting and monitoring the data. I then cleaned the dataset and analysed with Mr Paul Seed. I wrote the first draft of the manuscript, revised it following comments from the co-authors and am currently submitting for publication. I conducted ELISA analyses myself for the syndecan-1 and angiotensinogen biomarker quantification. Some PlGF measurements were also processed by research assistants Miss Zibusiso Mhangami and Miss Bethany Jones. Other biomarkers were analysed in the GSTT Viapath laboratory. I analysed the data with Mr Paul Seed. I wrote the first draft of the manuscript, received comments from the co-authors and submitted to the American Journal of Physiology- Regulatory, Integrative and Comparative Physiology, who have invited us to address the reviewers' comments and re-submit. I performed many of the vascular function assessments on the women enrolled in the PANDA study at Guy's and St Thomas' NHS Foundation Trust, with other assessments performed by the research midwives working on the study. I collated and cleaned the data, and then analysed it with Mr Paul Seed. I wrote the first draft of the manuscript which is currently being reviewed by the co-authors. All other chapters were written by myself and are my own work. Figures in Chapter 1 taken from other work are appropriately acknowledged.

PRESENTATIONS AND PUBLICATIONS ARISING FROM THIS WORK

Publications:

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Pregnancy And chronic hypertension: NifeDipine versus lAbetalol as antihypertensive treatment (the PANDA trial) *MacDonald Obstetric Medicine Meeting, Oxford*	September 2016
Second trimester vascular function parameters in women with chronic hypertension and their association with adverse maternal and perinatal outcomes *Second International Congress on Maternal Haemodynamics, Rome*	May 2016
Is ethnicity an independent risk factor for adverse perinatal outcomes in women with chronic hypertension? *London Specialty School of Obstetrics and Gynaecology Conference, London*	March 2016
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ABBREVIATIONS LIST

ACCT	Anglo-Cardiff Collaborative Trial
ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitor
ACR	Albumin: creatinine ratio
ADH	Anti-diuretic hormone
AGTCR	Angiotensinogen: creatinine ratio
AIX	Augmentation index
AIX-75	Augmentation index adjusted to a heart rate of 75 beats per minute
ALLHAT	Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial
AMD	Adjusted mean difference
ARBs	Angiotensin receptor blockers
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
BMI	Body mass index
BP	Blood pressure
CAFÉ	Conduit Artery Functional Endpoint study
CAP	Central aortic pressure
CHIPS	Control of hypertension in pregnancy study
CHT	Chronic hypertension
CI	Confidence interval
CMACE	Centre for Maternal and Child Enquires
CONSORT	Consolidated Standards of Reporting Trials
DBP	Diastolic blood pressure
ELISA	Enzyme-Linked Immunosorbent Assay
ENTIS	European Network of Teratology Information
FACT	Folic Acid Clinical Trial
FASTER	First- and Second-Trimester Evaluation of Risk Trial
FDA	Food and Drug Administration

FGR	Fetal growth restriction
GLS	Generalised Least Squares regression
GROW	Gestation Related Optimal Weight
HELLP	Haemolysis, elevated liver enzymes and low platelets syndrome
HYPITAT	Hypertension and Pre-eclampsia Intervention Trial At Term
HYPITAT II	Hypertension and Pre-eclampsia Intervention Trial At Term 2
ICD- 9 CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IQR	Interquartile range
ISRCTN	International Standard Registered Clinical/soCial sTudy Number
ISSHP	International society for the study of hypertension in pregnancy
IV	Intravenous
LSCS	Lower segment caesarean section
MBRRACE-UK	Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK
MELR	Mixed Effects Logistic Regression
MHRA	Medicines and Health Regulatory Authority
MR	Modified release
NICE	National Institute for Health and Care Excellence
NHS	National health service
OR	Odds ratio
PANDA	Pregnancy and Chronic Hypertension: Nifedipine versus Labetalol as Antihypertensive Treatment
PCR	Protein: creatinine ratio
PELICAN	Pre-EcLampsIa and the Clinical ApplicatioN of PLGF
PHOENIX	Placental growth factor to assess and diagnose hypertensive pregnant women
PlGF	Placental growth factor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols

PWV	Pulse wave velocity
RAAS	Renin angiotensin aldosterone system
RAS	Renin angiotensin system (organ specific)
RCT	Randomised controlled trial
REC	Regional Ethics Committee
RR	Risk ratio
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
sFLT-1	Soluble fms-like tyrosine kinase-1
SGA10	Small for Gestational Age (<10th birthweight centile)
SPE	Superimposed pre-eclampsia
SPRINT	Systolic blood pressure intervention trial
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
THIN	The Health Improvement Network
UK	United Kingdom
USA	United States of America
VEGF	Vascular endothelial growth factor

ABSTRACT

This thesis examines maternal and perinatal outcomes in pregnancy complicated by chronic hypertension. National guidance highlights the paucity of data from randomised controlled trials to guide choice of antihypertensive treatment for chronic hypertension in pregnancy. I performed a systematic review/meta-analysis of all randomised controlled trials comparing antihypertensive agents to non-active treatment/other antihypertensive agents for treatment of chronic hypertension in pregnancy. I demonstrated that antihypertensive agent use was associated with substantial reduction in the incidence of severe hypertension, but no significant differences in other maternal/perinatal outcomes were observed. The pathophysiology underpinning the increased risk of adverse maternal/perinatal outcome in women with chronic hypertension is poorly understood and likely to be multifactorial. I undertook a cohort study of 4481 pregnancies in women with chronic hypertension and assessed the impact of maternal characteristics on adverse perinatal outcome. Black ethnicity was strongly associated with adverse perinatal outcome. I conducted a randomised controlled feasibility study to compare labetalol and nifedipine for treatment of chronic hypertension in pregnancy. Feasibility of recruitment was confirmed and effectiveness of labetalol and nifedipine to control mean blood pressure to target examined. Outside pregnancy, Black women are recommended calcium-channel blockers as first-line antihypertensive treatment. I observed differences in treatment effect between ethnic groups and highlighted areas requiring further investigation. A nested mechanistic study within the trial demonstrated differences in placental/renal biomarker concentrations in women who developed superimposed pre-eclampsia, compared to those who did not, and between women of Black ethnicity compared to non-Black. Additional assessment of maternal vascular function across gestation showed no differences by ethnicity, but longitudinal variation in brachial blood pressure, central aortic pressure, pulse wave velocity, and augmentation index were demonstrated in women with chronic hypertension who developed adverse pregnancy outcome (superimposed pre-eclampsia and in those delivering small for gestational age infants) compared to those who did not.

CHAPTER 1 INTRODUCTION

1.1 Chronic hypertension in pregnancy- importance and challenges

Chronic hypertension is a common disorder affecting a quarter of the UK's adult population.[1] It may be primary, with no identifiable cause found, or secondary to another underlying medical condition (e.g. chronic kidney disease). Diagnosing chronic hypertension when it first occurs in an individual is a challenge, as it is not associated with a set of signs and symptoms and is instead most commonly detected following incidental blood pressure measurement. Chronic hypertension causes significant cardiovascular and cerebrovascular morbidity and mortality.[2,3] If left untreated, the risk of morbidity and mortality is accelerated.[4]

The prevalence of chronic hypertension in pregnancy is rising due to increasing maternal age and the global obesity epidemic.[5,6] The current incidence of chronic hypertension in pregnancy is estimated at 3%, making it the most common pre-existing medical disorder that directly impacts maternal and fetal wellbeing.[7] The disorder is associated with adverse maternal and perinatal outcomes such as superimposed pre-eclampsia, perinatal mortality, fetal growth restriction and preterm birth.[8] Pregnancy offers a screening opportunity for chronic hypertension, as routine blood pressure monitoring is incorporated into standard antenatal care and many women may not have had their blood pressure measured prior to pregnancy.

There are many physiological mechanisms that play a role in blood pressure homeostasis. Although variation in these mechanisms have been implicated, no unifying pathophysiological pathway has been identified.[9] The physiological changes associated with pregnancy cause a statistically significant reduction in blood pressure of 5 to 10 mmHg with the nadir in the second trimester.[10] However, these data are derived from small numbers of women[11,12] and not all studies agree, with a study reported by Nama and colleagues (2011) observing steady increase in blood pressure across gestation in low risk women.[13] Data from the Pregnancy Physiology Pattern Prediction Study (4P Study; ISRCTN10838017), which aimed to recruit 1000 low risk pregnant women should offer further insight into the clinical significance of reduction in blood pressure during pregnancy. The impact of chronic hypertension on the ability of the maternal vasculature to respond to these changes and the relationship between maladaptation and adverse outcome is not fully understood. Demographic and environmental risk factors associated with chronic hypertension have been identified such as age, smoking, obesity and ethnicity. Investigation of these risk factors and their association with adverse

maternal and perinatal outcomes would focus research prioritisation and guide choice of potential interventions.

Internationally guidelines vary for the management of chronic hypertension in pregnancy.[14] Recent evidence from the CHIPS study (Control of Hypertension In Pregnancy Study, 2015) has highlighted the maternal benefit of 'tight' (to a diastolic target of 85 mmHg) control of blood pressure on the risk of severe hypertension without an increase in perinatal adverse outcomes.[15] Current guidelines point to the lack of evidence from randomised controlled trials to guide antihypertensive prescription in pregnancy complicated by chronic hypertension.[16] With an ageing maternal population, rising obesity rates and advances in reproductive medicine, many more women with chronic hypertension are becoming pregnant and exploration of the most effective, safe and efficacious antihypertensive agents for treatment of this condition in pregnancy warrants investigation.

1.1.1 Definition of chronic hypertension in the non-pregnant population

Blood pressure is quantified as the systolic and diastolic arterial pressures in millimetres of mercury (mmHg). The systolic pressure represents the peak pressure during left ventricular systole and the diastolic pressure represents the pressure while the left ventricle is relaxed during diastole.[17] It is most commonly measured at the brachial artery using manual or automated cuff devices.[18] Chronic hypertension is defined as sustained raised arterial blood pressure. Blood pressure is normally distributed in the general population.[1] The thresholds used for diagnosis are defined as the level of blood pressure above which treatment will reduce the development or progression of cardiovascular disease, but in the absence of end organ damage this is set at blood pressures >140/90 mmHg.[1] Symptoms, if present, can include headache, tinnitus, vertigo or syncope. If severe hypertension is present at diagnosis then treatment should be initiated immediately, but otherwise it is recommended that the diagnosis should be confirmed following analysis of 24-hour ambulatory blood pressure monitoring.[1,19,20]

1.1.2 Definition of chronic hypertension in pregnancy

The International Society for the Study of Hypertension in Pregnancy defines chronic hypertension in the context of pregnancy, as a condition diagnosed prior to the last menstrual period or following two blood pressure readings with a systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg prior to 20 weeks' gestation.[21] Pregnancy presents a screening

opportunity for hypertension, as longitudinal blood pressure monitoring is a routine aspect of antenatal care, with the first reading taken in the first trimester and repeat readings taken throughout pregnancy until the woman is discharged from midwifery care in the post-partum period.[22]

The importance of defining the diagnosis in pregnancy lies in the clinical implications and subsequent management. Pregnancy can be complicated by gestational hypertension or de novo hypertension as a feature of pre-eclampsia, both conditions that are diagnosed after 20 weeks' gestation and should resolve after delivery. Pre-eclampsia can complicate chronic hypertensive pregnancy, but is described in this circumstance as superimposed and can be more difficult to confirm due to the pre-existing hypertension.[16] It is important to monitor blood pressure closely in the post-partum period if de novo hypertension is revealed in pregnancy, as the physiological fall in blood pressure (described in more detail below) may have masked underlying pre-existing chronic hypertension in the first and second trimester that had not previously been recognised.[23]

1.1.3 Prevalence of chronic hypertension in non-pregnant populations

The World Health Organisation estimated in 2008 that 40% of adults aged 25 years and above had been diagnosed with chronic hypertension globally; the number of people with the condition increased from 600 million in 1980 to 1 billion in 2008.[24] The increasing prevalence of chronic hypertension is thought to relate to an ageing population, the rise in obesity and other environmental risk factors.[4] It is estimated that the prevalence is lower in high income countries affecting 25-35% of the adult population.[1,4]

A population study conducted by Bateman and colleagues (2012) estimated prevalence of hypertension amongst women in their reproductive years (20 to 44 years) to be 7.7%.[25] It is unclear why this is more than double the estimated prevalence observed in pregnancy, but may relate to fewer women becoming pregnant once they have a diagnosis of chronic hypertension, or hypertension being diagnosed after a woman's family is complete. Risk factors for hypertension amongst this cohort included: older age, Black ethnicity, diabetes mellitus, chronic kidney disease and obesity. Another study examining prevalence of medical disorders amongst women seeking contraception in the USA by Champaloux and colleagues (2015), found an 8.3% prevalence of chronic hypertension.[26] Interestingly, when they examined the age associated prevalence, only 2.5% of those aged 15-34 years, but 15.6% of

those aged 35-44 years had chronic hypertension. This study is subject to selection bias, as women with medical conditions that impact pregnancy outcome may be more likely than normotensive women to seek contraception to prevent pregnancy and its associated complications.[26]

Ethnic variation in the prevalence of hypertension is reported internationally across all ages and genders.[4,27,28] The World Health Organization reports that, globally, the prevalence of hypertension is highest in Africa (46%).[4] An American study published by Geronimus and colleagues (2007), found that men and women of Black ethnicity were at much greater risk of developing hypertension and at a younger age than men and women of White ethnicity.[27] Additionally, they observed that prevalence of hypertension amongst adults aged 15 to 65 years, increased most rapidly in women and those of Black ethnicity.[27]

1.1.4 Prevalence of chronic hypertension in pregnancy

The prevalence of chronic hypertension in pregnancy is estimated to lie between 1 and 5%.[29-31] There is global and national variation in prevalence as found in the non-pregnant population. In addition, due to disparity in the definition used for diagnosis and errors in coding in medical databases, incidence reported in population studies are likely to underestimate the true prevalence.[29,32] A recent study of UK primary care data by Cea Soriano and colleagues (2014), reported that 1.3% of their 148,554 cohort of completed pregnancies had a diagnosis of pre-existing hypertension before their last menstrual period, but this does not include the women who had miscarriages (known to be increased in those with chronic hypertension), or women diagnosed with chronic hypertension in pregnancy.[31] This study also reported that women with pre-existing hypertension were more likely to be obese, have diabetes mellitus, hyperlipidaemia, or hypothyroidism.[31] Bateman and colleagues (2012) conducted a population study in USA using the Nationwide Inpatient Sample from 1995-2008 (56,494,634 deliveries), and found chronic hypertension increased from 1.0% in 1995/1996 to 1.8% in 2007/2008.[29] Compared to women without a diagnosis of chronic hypertension, the cohort with chronic hypertension were older and more likely to have other medical comorbidities.[29]

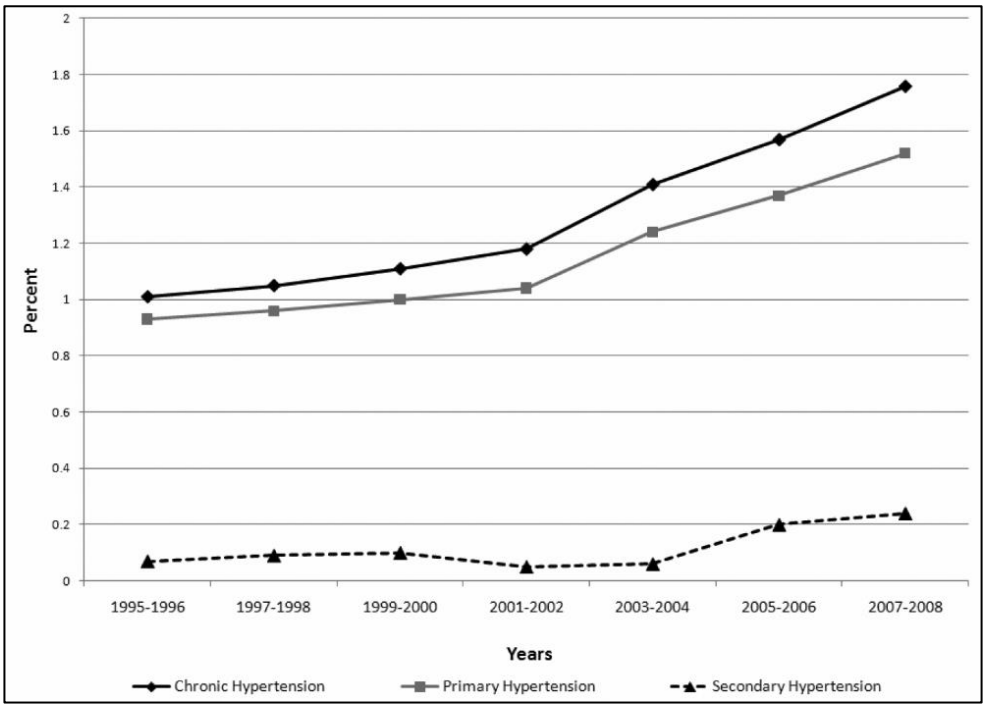


Figure 1.1 Nationwide Inpatient Sample trends in age-adjusted prevalence of chronic hypertension (primary and secondary hypertension) from 1995-1996 to 2007-2008, as published by Bateman and colleagues (2012)[29]

The prevalence of chronic hypertension in pregnancy is rising for several reasons. The overall increase in maternal age is likely to make a large impact.[33,34] A study by Matthews and colleagues (2009) reported that the maternal age at first birth had increased significantly between 1970 and 2006 in 14 countries studied with the range of mean increase in the order of 2.9 (Sweden) to 4.6 (Denmark) years.[5] Data from the National Vital Statistics System in USA (2015), demonstrate a reduction in the birth rate of women aged under 30 years, but an increase in those aged 30 to 44 years.[33,35] This is echoed by the findings of the report for previous years.[35] Data from the Office of National Statistics in the UK suggest a similar rise in the mean age of women giving birth.[36]

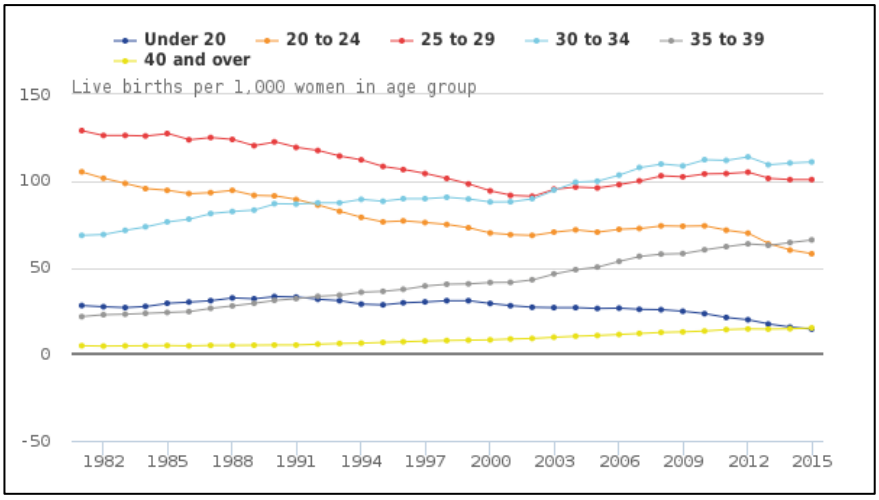


Figure 1.2 Data from the Office of National Statistics regarding fertility rates in the United Kingdom 1981 to 2015 presented by age range[36]

Another factor contributing to the rise in prevalence of chronic hypertension in pregnancy is the global obesity epidemic.[6,37] In the USA in the 1970s, the proportion of women aged 20 to 39 years with a body mass index greater than 30 kg/m^2 was 10%; by 1990 this had risen to 15% and by the mid-2000s it was more than 25%.[38] In the UK, the proportion of women classified as obese was estimated at 18-26%.[6] A UK study by Knight and colleagues (2008) of women with morbid obesity found that the incidence of chronic hypertension was 6% in pregnant women with a body mass index greater than 50 kg/m^2 compared to only 1% in those with a mean body mass index below 50 kg/m^2.[39]

1.1.5 Associated complications of chronic hypertension in the non-pregnant population

Chronic hypertension is an important preventable cause of morbidity and mortality.[1] It is strongly associated with an increased risk of cardiovascular disease and cerebrovascular disease in addition to renal disease and cognitive decline.[1] A recent study by Rapsomaniki and colleagues (2014) found that amongst 83,098 cardiovascular disease presentations, the association of systolic hypertension was greatest for intracerebral haemorrhage, subarachnoid haemorrhage and stable angina, though the risk of all adverse cardiovascular outcomes was increased compared to normotensive individuals.[40]

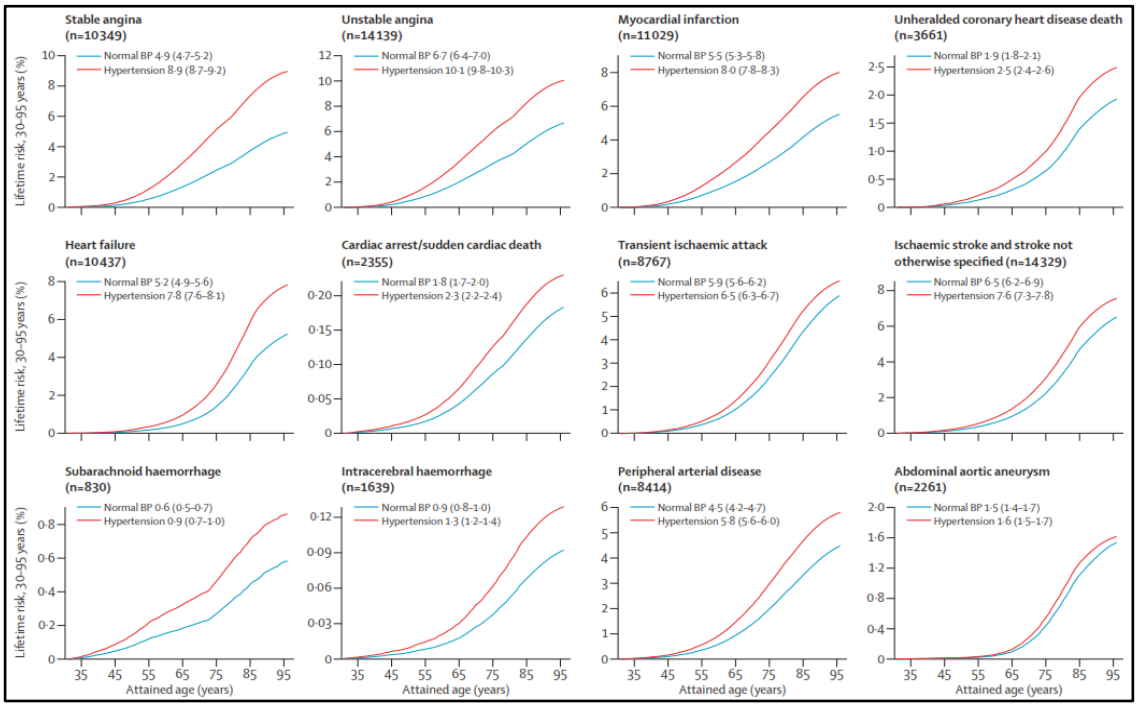


Figure 1.3 Rapsomaniki and colleagues (2014): Lifetime risk (95% confidence interval) of 12 different cardiovascular diseases at 30 years of age in people with hypertension or normal blood pressure [40]

Globally nearly one third of all deaths per year are due to cardiovascular disease; of these, over half are related to complications of hypertension.[41,42] Chronic hypertension accounts for at least 45% of deaths from ischaemic heart disease and 51% of deaths from stroke (ischaemic and haemorrhagic).[41]

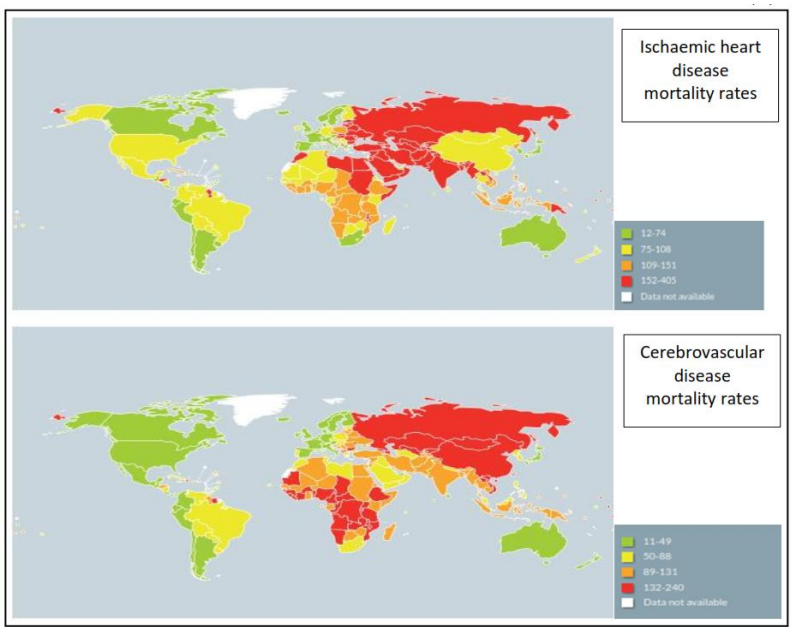


Figure 1.4 Heat map from the World Health Organisation demonstrating the global ischaemic heart disease and cerebrovascular disease mortality rates (age standardised, per 100,000)[41]

1.1.6 Adverse maternal and perinatal outcomes associated with chronic hypertension

Chronic hypertension is one of the most common pre-existing medical disorders in pregnancy. It is associated with a significant increase in adverse maternal and perinatal outcome. Mothers with chronic hypertension are at increased risk of pregnancy-specific morbidity such as superimposed pre-eclampsia,[8,29,43-47] caesarean section,[8,29,46] placental abruption,[44,48], prolonged hospital stay[29] and maternal mortality.[29,49-51] They are also at an increased risk of other end-organ damage and complications: stroke,[50,52] pulmonary oedema,[29,50,51] and acute kidney injury[29,50,51]. Adverse perinatal outcomes include: prematurity,[8,29,45] fetal growth restriction,[30,45,53,54] neonatal unit admission,[8,45] and perinatal death.[8,29,55]

A recent systematic review of chronic hypertension and pregnancy outcomes by Bramham and colleagues (2014), reported a 26% incidence of superimposed pre-eclampsia from meta-analysis of 38 studies.[8] This study additionally compared data from US population studies to calculate the relative risk of superimposed pre-eclampsia in women with chronic hypertension (relative risk 7.7, 95% confidence interval 5.7 to 10.1) compared to pregnant controls.[8] The other outcomes meta-analysed in this study included: caesarean section rate 41%, preterm birth (<37 weeks' gestation) 28%, birthweight <2500g 17%, neonatal intensive care admission 21% and perinatal death rate of 4%. The study was unable to assess other maternal and perinatal adverse outcomes due to inconsistencies in the reported outcomes of the studies identified.

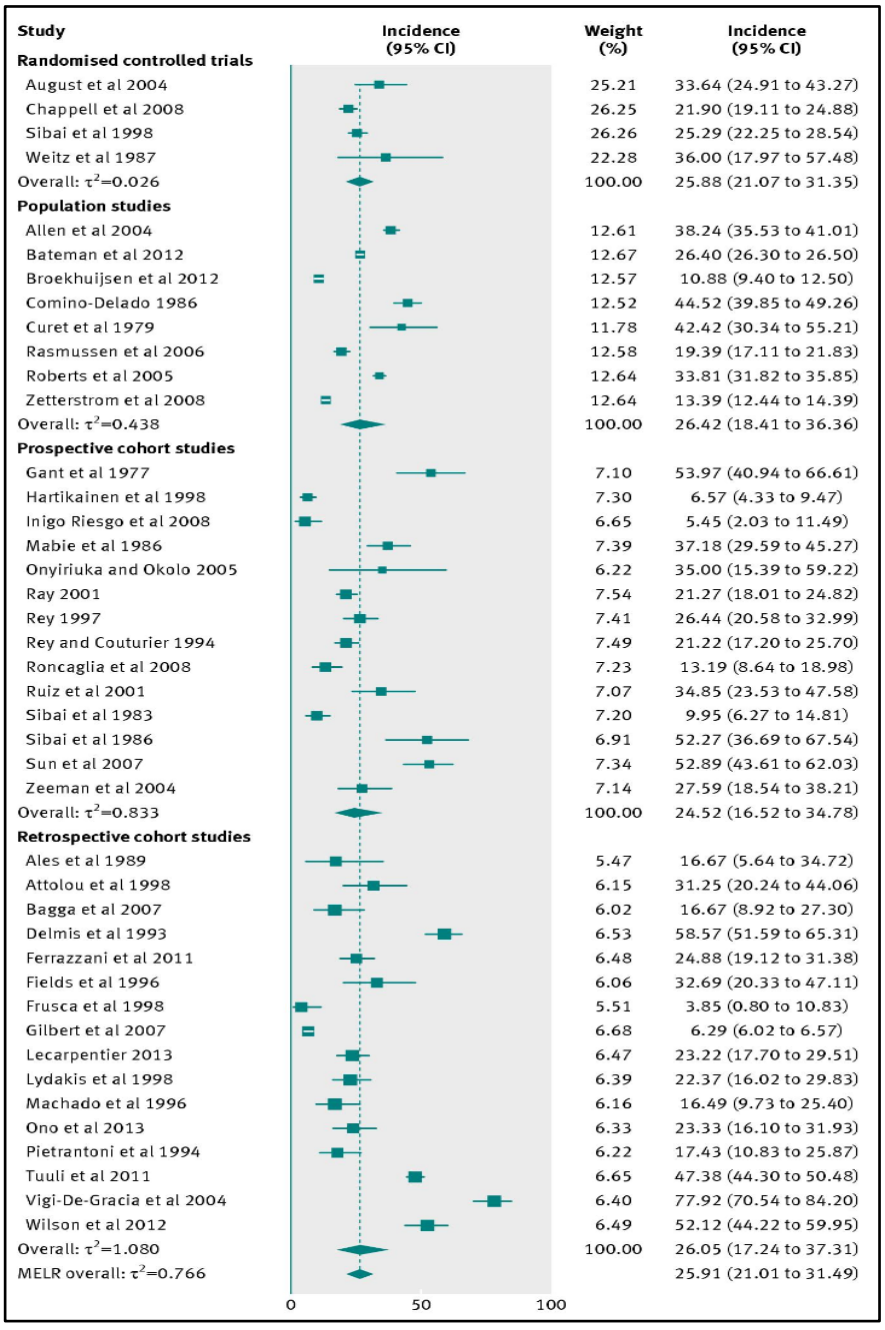


Figure 1.5 Bramham and colleagues (2014), forest plot stratified by study design of studies assessing incidence of superimposed pre-eclampsia in women with chronic hypertension. (MELR = mixed effects logistic regression)[8]

Bateman and colleagues (2012) compared maternal and perinatal outcomes in their previously described population study between women who did and did not have a diagnosis of chronic hypertension (1995 to 2008). Maternal outcomes reported included: superimposed pre-eclampsia odds ratio (OR) 10.07 (95% confidence interval 9.68 to 10.48), stroke/cerebrovascular event OR 5.41 (95% confidence interval 4.27 to 6.86), acute kidney injury OR 14.62 (95% confidence interval 12.06 to 17.73), pulmonary oedema OR 9.26 (95%

confidence interval 6.67 to 12.85), length of stay greater than six days OR 6.73 (95% confidence interval 6.21 to 7.29), and in-hospital mortality OR 6.20 (95% confidence interval 3.33 to 11.54). The perinatal outcomes reported included: stillbirth OR 2.31 (95% confidence interval 2.11 to 2.53), poor fetal growth OR 3.00 (95% confidence interval 2.83 to 3.19) and spontaneous preterm birth before 37 weeks' gestation OR 3.01 (95% confidence interval 2.88 to 3.14). This study also compared outcomes in a sub-group analysis of women with primary versus secondary hypertension and concluded that secondary hypertension was associated with a greater risk of all adverse outcomes than primary hypertension. The limitations of this study include identification of maternal and perinatal outcome from ICD-9 CM coding and difficulties in identifying women with mild chronic hypertension. The outcome of 'poor fetal growth' ICD-9 CM code 656.6x has high specificity for identifying the babies born with a birthweight below the 10th centile, but a low sensitivity as many babies will be misclassified.[56] Additionally the authors concede that certain potential confounders such as ethnicity and body mass index could not be adjusted for in the analysis.

Hypertension in pregnancy remains one of the leading causes of maternal death globally.[57] However the recent MBRRACE-UK report showed that maternal deaths in the UK from pre-eclampsia are at their lowest incidence to date, with the death rate at less than one per million maternities for the first time since maternal deaths have been systematically counted.[58] An editorial by Shennan and colleagues (2017) reported that the proportion of maternal deaths from hypertensive disorders of pregnancy was 2·8% in the UK (2012 to 14),[58] 7·4% in the USA (2011 to 13),[59] and 14% globally (2013)[60].[61] In 2011 the Centre for Maternal and Child Enquires (CMACE, now known as MBRRACE-UK) triennial report highlighted amongst its key recommendations the importance of treating systolic hypertension above 150 mmHg, as inadequate blood pressure control was a key factor in the maternal deaths from hypertensive disorders during that time period.[49] This underlines the importance of epidemiological studies such as MBRRACE-UK and demonstrates that death from hypertensive disorders of pregnancy is preventable.[61] Another study by Leffert and colleagues (2015) evaluated the trends and associations of hypertensive disorders in pregnancy with stroke risk in an American population study.[62] They found that between 1994-1995 and 2010-2011 the rate of stroke with hypertensive disorders of pregnancy doubled from 0.8 to 1.6 per 10,000 pregnancy hospitalisations, compared with a more modest increase in the rate of stroke from 2.2 to 3.2 per 10000 pregnancy hospitalisations not affected by hypertensive disorders.[62] This increase is of particular interest given that a 10-year decline in overall stroke prevalence among older

adults in the USA has been reported.[63] Unfortunately this study did not subdivide the women with hypertensive disorders of pregnancy to allow exploration of the impact of chronic hypertension and pre-eclampsia, rather than gestational hypertension alone.

Assessing the impact of chronic hypertension on adverse perinatal outcomes is complex. The impact of increased incidence of superimposed pre-eclampsia on adverse perinatal outcome is significant, as assessed by Chappell and colleagues (2008).[45] This UK-based study compared the proportion of infants with birthweight centiles below the 5th and 10th percentile in women with chronic hypertension who did and did not develop superimposed pre-eclampsia; they found that the risk ratio of birthweight centile <10th was 2.30 (95% confidence interval 1.85 to 2.84) in women who developed superimposed pre-eclampsia compared to the women who did not and even more strikingly the risk ratio of birthweight centile <5th was 2.94 (95% confidence interval 2.27 to 3.80) in the women who developed superimposed pre-eclampsia compared to those who did not.[45] It is important to note that within this cohort 21% of babies born to mothers who did not develop superimposed pre-eclampsia were born with a birthweight <10th centile, which is double what would be expected in the general pregnant population.[45] This underlines chronic hypertension as an independent risk factor for fetal growth restriction. Chappell and colleagues additionally report a stillbirth rate of 2.1% in this cohort, three and a half times that of the UK general pregnant population (0.6%).[36,45] The difference in stillbirth rate in women who did and did not develop superimposed pre-eclampsia did not reach statistical significance.[45]

Another population based study from Canada by Allen and colleagues (2004) examined the effect of hypertensive disorders in pregnancy on small for gestational age infants and stillbirth.[54] They analysed data from 135,466 pregnancies and reported that the adjusted odds ratio of small for gestational age was significantly increased for all hypertensive disorders of pregnancy compared to the Canadian general pregnant population. However, the adjusted odds ratio of stillbirth was only significantly raised in women with chronic hypertension (aOR 3.2, 95% CI 1.9 to 5.4) when rates were compared with the normotensive pregnant population.[54]

There is an ongoing debate regarding the association between antihypertensive agent use and fetal growth restriction.[64] There is additionally no consensus regarding blood pressure thresholds above which chronic hypertension should be treated in pregnancy.[14] A meta-

analysis of changes in mean arterial pressure and fetal growth restriction in pregnancy hypertension conducted by von Dadelszen and colleagues (2000), concluded that treatment-induced falls in maternal blood pressure may adversely affect fetal growth. However, only three randomised controlled trials (including 350 women) comparing antihypertensive treatment to no treatment/placebo in women with chronic hypertension were included in the primary analysis. Differences in the pathophysiology of chronic hypertension and de novo hypertension as seen in gestational hypertension and pre-eclampsia may influence these findings. A systematic review of treatment of hypertensive disorders in pregnancy by Magee and colleagues (1999), did not demonstrate an association between antihypertensive use and small for gestational age infants (odds ratio 1.28, 95% confidence interval 0.69 to 2.36), but again this study was limited by the number of trials available for analysis.

Studies assessing the impact of maternal characteristics on the risk of adverse perinatal outcome are limited. Further investigation of the factors that contribute to adverse perinatal outcome in women with chronic hypertension are needed. An understanding of these risk factors would guide research into the mechanisms, pathophysiology and potential treatment targets for women with chronic hypertension in pregnancy. Definitions of morbidity change over time and implications of diagnoses on long-term maternal and infant health need to be considered. An example of this is the definition of small for gestational age and fetal growth restriction; the former is widely accepted as neonatal birthweight below the 10th percentile and is associated with less morbidity and mortality than fetal growth restriction, which has recently been defined as birthweight below the 3rd percentile.[65] Further studies using these definitions in pregnancy complicated by chronic hypertension are warranted.

1.2 The physiology of blood pressure and pathophysiology of hypertension

1.2.1 The physiology of blood pressure

Blood pressure describes the maximum (systolic) and minimum (diastolic) pressure of the systemic arterial circulatory system. Blood is pumped from the left ventricle in cardiac systole into the aorta and then onto the arterial system before entering the peripheral capillaries and finally the venous system.[17] The maximum pressure in the arteries occurs during cardiac systole and the minimum during diastole when the left ventricle is relaxed. The haemodynamic factors primarily affecting blood pressure include blood volume, cardiac output and systemic vascular resistance.[17] There are many mechanical, hormonal and neurological influences on

these haemodynamic factors that achieve homeostasis in blood pressure in normotensive individuals. Consequently, an imbalance in haemodynamic factors can lead to hypertension (or hypotension) and an understanding of the pathophysiology unpinning these changes offers insight into potential treatment targets.

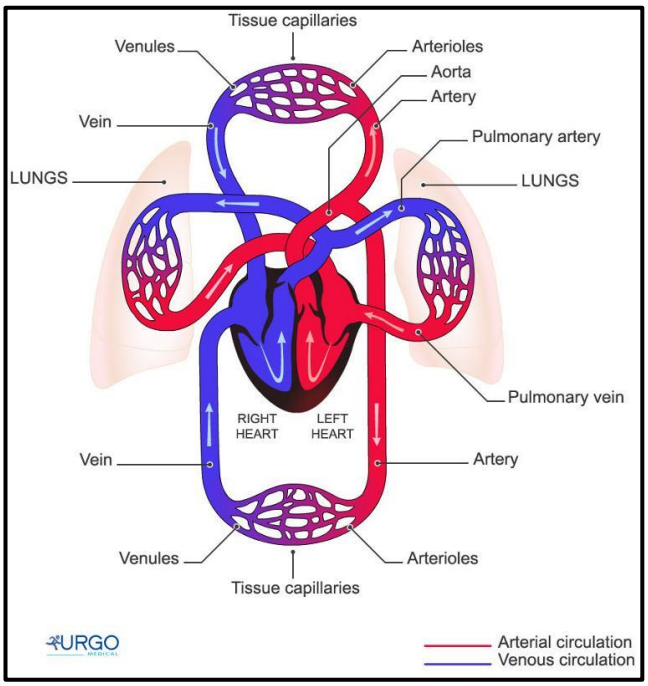


Figure 1.6 Diagram of the human circulatory system highlighting in red the left ventricle and the arterial systemic circulation which establish blood pressure (Boston University School of Public Health)[66]

Our understanding of the endogenous mechanisms controlling blood pressure is incomplete, but some key influences are well described. The systemic renin-angiotensin-aldosterone system (RAAS) is hormonally based and regulates plasma sodium concentration and consequently arterial blood pressure.[67] Renin is secreted into the circulation primarily by the kidney (though it can be secreted by other organs) following conversion from prorenin (an intracellular protein) in the juxtaglomerular cells. It acts to cleave angiotensinogen (produced by the liver) into angiotensin I. Angiotensin I is then converted into the active vasoconstrictor angiotensin II by angiotensin-converting enzyme (ACE). ACE is found in endothelial cells of capillaries throughout the body, especially within the lungs and additionally in the epithelial cells of the kidneys. Angiotensin II causes the arterioles to constrict leading to increased blood pressure. Aldosterone secretion from the adrenal cortex is also stimulated by angiotensin II. Aldosterone acts to increase sodium reabsorption in the tubular epithelial cells of the kidneys back into the blood and increases renal potassium excretion.[17] Aldosterone secretion can also be stimulated by high potassium, which plays a role in the pathophysiology of some secondary

causes of hypertension. Sodium retention increases intravascular fluid retention and consequently increases blood volume and indirectly increases blood pressure. [17]

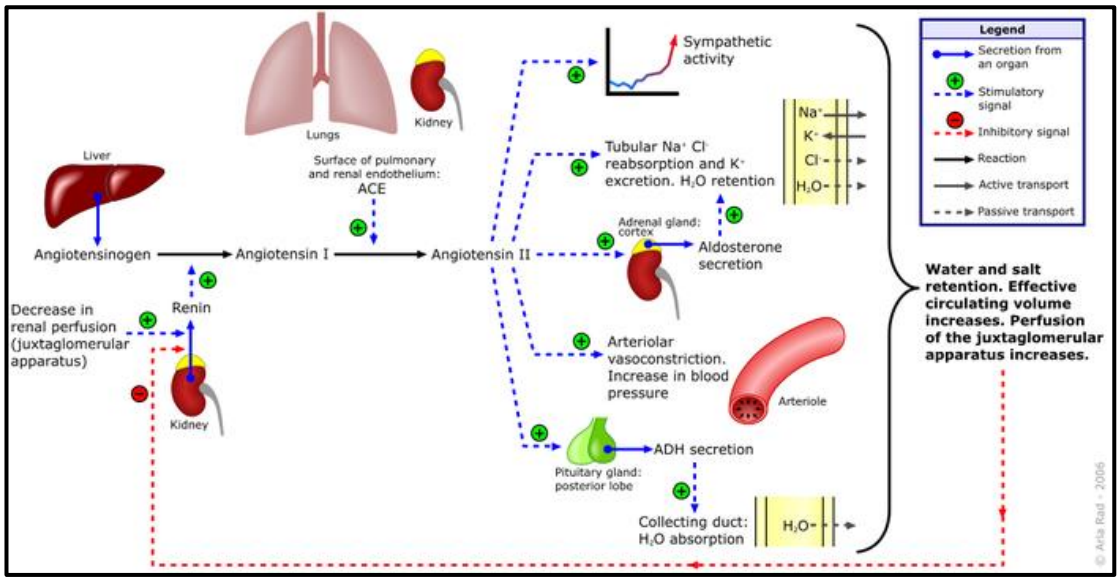


Figure 1.7 Schematic representation of the systemic renin-angiotensin-aldosterone system[68]

The autonomic nervous system also plays a role in blood pressure homeostasis.[17] One of the principal actions is via the baroreceptors that are located in the aortic arch and the carotid sinuses in addition to other circulatory sites. These mechanoreceptors are sensitive to stretch and provide a rapid negative feedback loop via the central nervous system when blood pressure is increased, lowering heart rate and cardiac output, and consequently lowering blood pressure. If blood pressure is low, they act to increase heart rate and blood pressure. Baroreceptors also regulate secretion of renin and aldosterone, in addition to antidiuretic hormone (ADH). ADH (also known as vasopressin) is produced by the posterior pituitary gland. Its principal action is on the kidneys, causing water retention, but at very high levels it also causes vasoconstriction which in turn causes hypertension.[17] Atrial natriuretic peptide (ANP) is secreted by the cardiac atrial myocytes in response to increased atrial filling pressure. It stimulates excretion of sodium and water in the renal tubules and has a weak vasodilator effect.[17] Another group of hormones that interact with the autonomic nervous system are the catecholamines. Catecholamines such as adrenaline and noradrenaline are secreted by the adrenal medulla in response to stress and act on the sympathetic nervous system to cause the 'flight or fight' response. This response in turn causes increased heart rate and hence increased blood pressure.[17]

1.2.2 The pathophysiology of hypertension

The aetiology of primary hypertension is unclear. Primary hypertension describes chronically elevated arterial blood pressure without evidence of another causative disease process, but the disorder demonstrates strong associations with hereditable and environmental factors.[9,69] Animal models of genetic hypertension and human Mendelian forms of hypertension have provided insight into possible pathways that are disrupted in blood pressure homeostasis with most mechanisms relating to renal sodium reabsorption.[69] Genetic studies in humans have revealed some population specific information about disease susceptibility from genome-wide association studies.[70-72] However unpicking the effect of genetics from environmental risk factors, such as obesity, salt intake, smoking and alcohol intake, is complex.[9]

Dysfunction of the hormonal pathways influencing blood pressure homeostasis have been characterised as specific disease processes causing secondary hypertension, such as Cushing's and Conn's syndromes causing hyperaldosteronism; however no consistent alterations in the systemic RAAS have been implicated in the pathophysiology of primary hypertension.[73] On the contrary, marked heterogeneity in circulating renin and aldosterone levels exists in those with and without a diagnosis of hypertension.[67] Further exploration of the variation in renin concentration amongst individuals with primary hypertension has shown that the majority have normal or high plasma renin activity, but around one third have low or supressed renin.[67,73] Low plasma renin levels are associated with increased salt sensitivity and have been found more commonly in those of African or Caribbean ethnicity.[74,75] These initial studies of serum plasma renin activity have been corroborated by genetic studies linking specific genotypes to low renin hypertension.[76]

Variation in pathophysiology underpinning primary hypertension has been further elucidated through disparity in antihypertensive agent response. Antihypertensive agents targeting the RAAS, such as angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs), are considered most effective at controlling blood pressure and reducing morbidity and mortality in those of non-Black ethnicity.[1,77] However, evidence reported by Leenen and colleagues (2006) from the ALLHAT study (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (total participants n=18,102), demonstrated an increased risk of combined cardiovascular disease (risk ratio 1.13; 95% confidence interval 1.02 to 1.24) and stroke (risk ratio 1.51; 95% confidence interval 1.22 to 1.86) when lisinopril (ACE inhibitor) was prescribed as first-line antihypertensive treatment compared with

amlodipine (calcium-channel blocker) in Black participants (amlodipine n=3213 versus lisinopril n=3210).[78] A further secondary analysis of the ALLHAT study by Piller and colleagues (2006) also reported an increase in the risk of angioedema in Black participants prescribed lisinopril compared to amlodipine or chlorthalidone (diuretic).[79] More recently pharmacogenetic studies have aimed to provide insight into the ethnic variation in drug response, but quantifying the heritable contribution to drug response variability makes the clinical translation of such studies a challenge.[80]

	Systolic/diastolic blood pressure reduction*		
Drug category	European ancestry	African ancestry	Difference†
Calcium blockers	15.3/12.6	16.9/13.3	2.4/0.6
	(14.7, 15.9)/(12.3, 12.9)	(16.0, 17.7)/(12.9, 13.8)	(3.4, 1.3)/(1.2, 0.0)
Diuretics	11.5/9.1	15.0/10.7	3.5/1.5
	(9.5, 13.4)/(8.1, 10.1)	(13.1, 17.0)/(9.5, 11.9)	(6.4, 0.5)/(3.1, −0.1)
ACE-i	12.8/11.4	8.5/8.0	−4.6/−3.0
	(11.7, 13.9)/(10.8, 12.0)	(7.0, 9.9)/(7.1, 8.9)	(−2.7, −6.5)/(−1.9, −4.1)
β-Blockers	11.7/11.3	5.9/9.5	−6.0/−2.9
	(10.2, 13.3)/(10.5, 12.1)	(4.2, 7.6)/(8.5, 10.4)	(−3.6, −8.3)/(−1.6,−4.2)

Figure 1.8 Brewster and colleagues (2013): Differences in clinical efficacy of antihypertensive drugs in ancestry groups[81]
*Data depicted are pooled estimates (95% confidence intervals) from systematic reviews.[82,83] ACE-i, angiotensin converting enzyme inhibitors. *Mean blood pressure reduction (mmHg). †The depicted difference is the weighted pooled difference in response between ancestry groups, with positive values indicating a greater response in patients of African ancestry and negative values indicating a greater response in patients of European ancestry.*

Hypertension has previously been demonstrated to impair baroreceptor modulation of heart rate.[84-86] However, primary hypertension does not appear to alter the baroreflex sympathetic nervous system activity.[87] More recently research has re-evaluated the association of sympathetic nervous system activity and hypertension.[88] Novel device-based therapeutic interventions decreasing renal and systemic sympathetic nervous system activity have successfully reduced hypertension in drug-resistant individuals,[88] however, the long-term success of renal denervation has not been repeated in larger more recent trials[89] and this treatment is not yet recommended by national guidelines.[1] Perhaps the most important association between sympathetic activation and elevated blood pressure is in obesity related hypertension. Animal models of obesity demonstrate a variety of associations between adiposity and activation of the sympathetic nervous system contributing to the subsequent development of hypertension.[90-92] Given the international obesity epidemic, further investigation of the relationship between obesity and hypertension in humans is needed.

There are many causes of secondary hypertension. The relationship between secondary hypertension and the underpinning pathophysiology is usually clearer. The most common cause is chronic kidney disease.[17] The key role of the kidney in plasma volume homeostasis conveys a significant effect of renal dysfunction on blood pressure equilibrium. Examples of endocrinological causes of secondary hypertension include hyperaldosteronism (Conn's syndrome-an adrenal cortex tumour), excess glucocorticoid steroid production (Cushing's syndrome), or excess catecholamine secretion (phaeochromocytoma-tumour of the adrenal medulla), which cause hypertension through hormonal excess within the pathways that maintain blood pressure homeostasis.[17] There are many other less common causes of secondary hypertension which should be considered to ensure appropriate treatment in addition to blood pressure reduction with antihypertensive agents.

1.2.3 The physiology of blood pressure in pregnancy

The primary physiological change that occurs in pregnancy altering blood pressure homeostasis is marked vasodilatation of both the systemic and renal vasculature.[93] This vasodilation occurs as early as five weeks' gestation and is estimated to reach its nadir in the second trimester with either a plateau or slow increase towards the end of the third trimester.[11] A recent study by Mahendru and colleagues (2014) in 54 women estimated changes in cardiac output and peripheral vascular resistance using a non-invasive inert gas re-breathing technique, prior to conception and subsequently at 6, 23, and 33 weeks during their low-risk pregnancies and at 16 weeks postpartum. The relationship between time before, during and after pregnancy between cardiac output and peripheral vascular resistance is demonstrated in Figure 1.9. A reciprocal relationship between cardiac output and peripheral vascular resistance during pregnancy was observed. Cardiac output increased from preconception measures into the second trimester, remained increased during the third trimester, and then decreased back to baseline by 16 weeks' postpartum. The peripheral vascular resistance decreased significantly from preconception levels by the second trimester, but increased in the third trimester and had returned to preconception values by 16 weeks postpartum.[11]

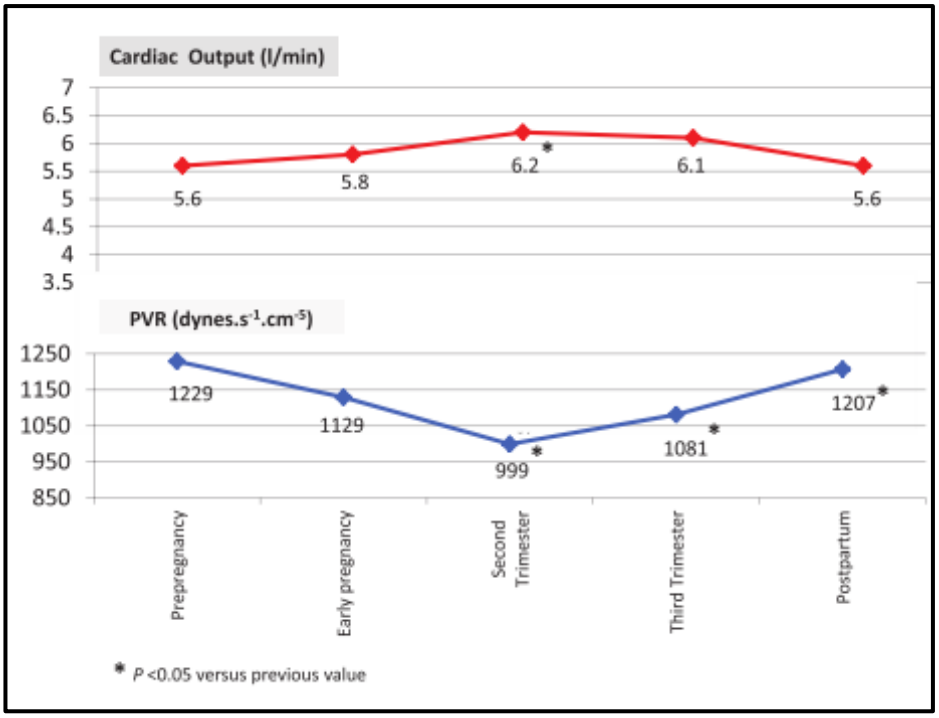


Figure 1.9 Mahendru and colleagues (2014): Longitudinal changes in cardiac output and peripheral vascular resistance from preconception to the postpartum period[11]

The marked vasodilation appears to relate to the rise in circulating oestradiol and progesterone;[94,95] however understanding of the mechanisms underpinning these changes is incomplete. Relaxin is a peptide hormone that has been shown to substantially rise in the maternal circulation during the first trimester before falling slightly across the second and third trimesters.[96,97] A study by Kristiansson and colleagues on a Swedish cohort of 200 pregnant women found a significant relationship between higher first trimester relaxin and progesterone levels (but not oestradiol) and lower systolic blood pressure levels in the second and third trimester.[98] They also noted lower relaxin levels in the first trimester were associated with subsequent diastolic blood pressure readings >90 mmHg.[98] Nitric oxide is a potent vasodilator that appears to play an important role in reproductive physiology;[99] however, studies conducted to date provide conflicting results regarding the role of nitric oxide in the vasodilation of pregnancy.[100,101] This may relate to the instability of nitric oxide ex vivo and the complex models required to estimate activity.[102]

Blood pressure, both systolic and diastolic, decrease in early pregnancy from pre-pregnancy values by 5 to 10 mmHg.[11,12] The nadir of gestational arterial pressure is likely to occur in the second trimester. The study conducted by Mahendru and colleagues (2014) of 54 women, demonstrated a significant fall in blood pressure measures from pre-conception levels as early as six to eight weeks' gestation. Interestingly they found the 16 week postpartum values of

blood pressure remained significantly lower than the pre-conception values and though the authors postulate that this may be because other studies compare gestational and postnatal blood pressure values, it seems probable that these findings require exploration in a larger cohort with evaluation of the impact of other hormonal influences such as breast feeding.[11] Grindheim and colleagues (2012) evaluated the impact of gestation on 57 women at 15, 23, 31 and 36 weeks' gestation and at six months postpartum, and demonstrated a nadir in blood pressure at 23 weeks' gestation, with six month postpartum levels significantly higher than gestational values.[12] Given the large number of demographic factors that influence blood pressure in normotensive women such as ethnicity, age and body mass index, the nadir of blood pressure readings is likely to vary depending on the sample of women studied and these findings serve primarily to highlight that raised blood pressure measures recorded before 20 weeks' gestation in women previously thought to be normotensive, are likely to represent underlying chronic hypertension.

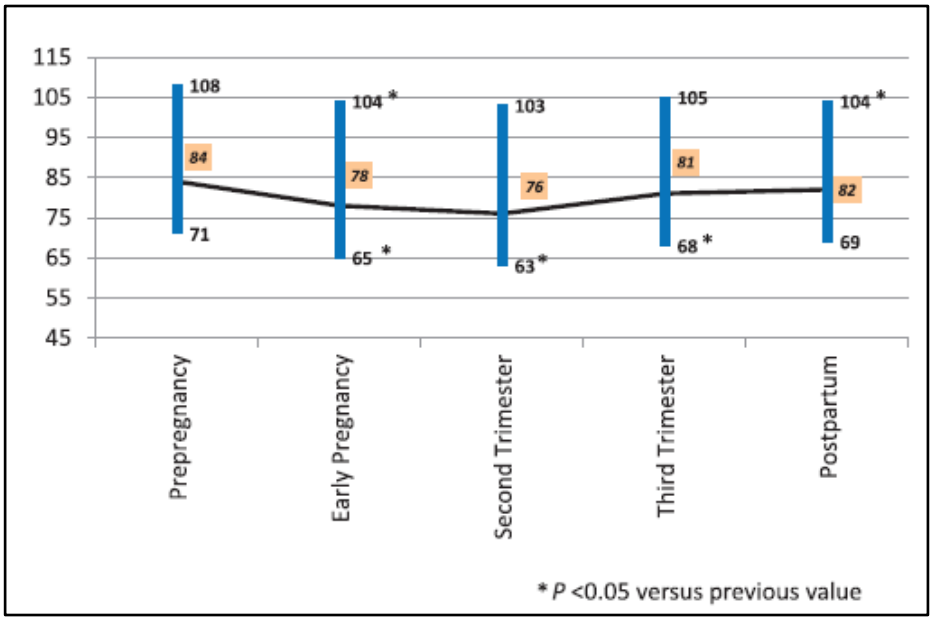


Figure 1.10 Mahendru and colleagues (2014): Serial blood pressures before, during and after pregnancy[11]

The RAAS is upregulated in pregnancy as early as the first trimester.[103] Renin is secreted by extra-renal sites such as the ovaries and maternal decidua, and increased oestrogen acts on the liver to increase circulating angiotensinogen.[104] This causes an increase in angiotensin II and aldosterone concentrations.[105] Angiotensin converting enzyme is the only RAAS component that has been demonstrated to fall during pregnancy.[106] Activation of the RAAS in pregnancy is thought to maintain blood pressure by aiding salt and water retention, when

maternal systemic and renal arterial dilation are creating a relatively underfilled circulatory system.[10] Despite the increase in systemic RAAS concentrations, normotensive pregnant women appear to be refractory to the increase in angiotensin II and its vasopressor effects. A study reported by Assali and colleagues (1961) used animal models to demonstrate that pregnant dogs and sheep required double the intravenous infusion of angiotensin II compared with non-pregnant female dogs and sheep to achieve the same vasomotor response.[107] A subsequent study in humans conducted by Gant and colleagues (1980), postulated that increased progesterone and prostacyclins found in pregnancy may decrease maternal sensitivity to angiotensin II.[108] There remains much about the role of the systemic RAAS in the normal physiology of pregnancy that is poorly understood.

1.2.4 Pathophysiology of chronic hypertension in pregnancy and superimposed pre-eclampsia

Women with uncomplicated chronic hypertension in pregnancy also demonstrate gestational fall in blood pressure. A longitudinal case-control study conducted by August and colleagues (1990) included 30 pregnancies in women with chronic hypertension and 14 normotensive pregnant controls. Mean blood pressure was compared prior to conception, and then at 10, 20, 28, 32 and 38 weeks' gestation between women with uncomplicated chronic hypertension in pregnancy (n=17), women with chronic hypertension who developed superimposed pre-eclampsia (n=13), and normotensive pregnant controls (n=14). In all women a gestational fall in blood pressure was observed in the first and second trimesters, with subsequent rise in the third trimester (Figure 1.11), but in women with superimposed pre-eclampsia, this increase was greater.[109] Another study by Tihtonen and colleagues (2007) demonstrated other gestational haemodynamic differences between women with chronic hypertension (n=20) and normotensive controls (n=30), including increased systemic vascular resistance index and pulse wave velocity.[110] Stroke volume index was significantly lower in the early second trimester in women with chronic hypertension compared to normotensive women, which led the investigators to conclude that women with chronic hypertension may have a reduced intravascular volume increase during pregnancy.[110]

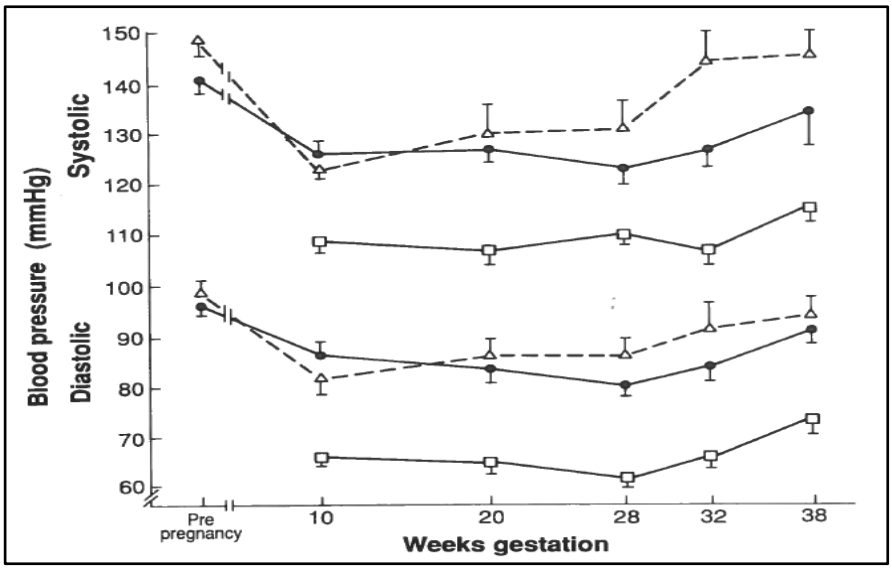


Figure 1.11 August and colleagues (1990): Serial changes in systolic and diastolic blood pressure in women with chronic hypertension and superimposed pre-eclampsia (open triangle), women with uncomplicated chronic hypertension (filled circle), and normotensive pregnant controls (open square)[109]

The mechanisms underpinning the increased incidence of pre-eclampsia in women with chronic hypertension are yet to be elucidated fully. It has been suggested that women at increased risk of pre-eclampsia have genetic, biochemical, and metabolic abnormalities that are similarly associated with chronic hypertension.[111] These abnormalities include a higher incidence of polymorphisms in the angiotensinogen gene, obesity, hypertriglyceridaemia, and insulin resistance. Variation in the RAAS has also been explored. The case control study conducted by August and colleagues (1990) quantified plasma renin activity and urinary aldosterone concentration in normotensive pregnant women and women with chronic hypertension who did and did not develop superimposed pre-eclampsia.[109] Plasma renin activity decreased significantly between 20 to 32 weeks' gestation in women who developed superimposed pre-eclampsia and increased significantly in normotensive pregnant controls. In women with uncomplicated chronic hypertension in pregnancy, plasma renin activity remained constant across gestation. Plasma renin activity was significantly lower in women with superimposed pre-eclampsia in the third trimester when compared to pregnant women with uncomplicated chronic hypertension and normotensive pregnant controls. Additionally this study found that urinary aldosterone concentrations were significantly lower in the third trimester in women with superimposed pre-eclampsia compared to both pregnant women without superimposed pre-eclampsia and normotensive pregnant controls.[109]

1.3 Current management strategies for chronic hypertension in pregnancy

1.3.1 Pre-pregnancy advice

Routine pre-pregnancy counselling for all women with pre-existing medical disorders is recommended by serial reports from MBRRACE-UK in order to optimise their medical condition prior to starting pregnancy.[49] This is of particular importance in women with chronic hypertension, given the associated increased risk of maternal and perinatal morbidity and mortality.[16] Discussion regarding potential change in antihypertensive treatment to agents that are safe in pregnancy and optimisation of blood pressure control are recommended.[7] General health advice and discussion of potential lifestyle and dietary changes that may benefit pregnancy outcome are also advised.[16]

Antihypertensive agents recommended in the non-pregnant population are outlined by the NICE guideline for the management of hypertension in adults;[1] however not all of these drugs are considered safe in pregnancy.[16] Outside of pregnancy, in those aged under 55 years of age (not of African or Caribbean family origin), ACE inhibitors or ARBs are recommended as first line treatment, and in those aged over 55 years or of African/Caribbean family origin, calcium channel blockers are recommended as first line treatment.[1] If ACE inhibitors, ARBs or chlorothiazide are taken and pregnancy is confirmed, change of treatment to an agent recognised as safe for use in pregnancy (see below) is recommended.[16]

1.3.2 Antenatal care pathways

Pregnancy complicated by chronic hypertension is considered high risk and obstetric consultant-led care is recommended in the UK. The number of antenatal visits will be tailored to each woman and dictated by maternal history and events within the pregnancy. A detailed history and examination should be taken at the first medical antenatal appointment to establish whether the hypertension is primary or secondary and if further investigations or other specialist referral in pregnancy are required. Pregnancy represents an opportunity to further promote dietary and lifestyle changes that could impact the disease process associated with chronic hypertension; it may also be the first time the condition is diagnosed, and it is therefore important to ensure appropriate investigations and follow up are instigated. Women with secondary hypertension may need additional specialist care in pregnancy from an Obstetric Physician, Nephrologist, Cardiologist, or Endocrinologist, depending on the secondary cause and its severity.

1.3.3 Prevention of superimposed pre-eclampsia

Chronic hypertension in pregnancy is associated with a four-fold increase in the risk of developing superimposed pre-eclampsia compared to the background pregnant population.[8] Changes in the platelet and clotting cascade that occur early in the pathogenesis of pre-eclampsia have led researchers to explore antiplatelet agents for prevention of pre-eclampsia. A Cochrane review of the trials examining the efficacy of aspirin in prevention of pre-eclampsia in high risk pregnancies, found a 17% risk reduction with aspirin use compared to no active intervention (46 trials, 32,891 women; relative risk 0.83, 95% confidence interval 0.77 to 0.89).[112] Reduction in the risk of preterm birth (29 trials, 31,151 women; relative risk 0.92, 95% confidence interval 0.88 to 0.97), fetal or neonatal deaths (40 trials, 33,098 women; relative risk 0.86, 95% confidence interval 0.76 to 0.98) and small-for-gestational age babies (36 trials, 23,638 women; relative risk 0.90, 95% confidence interval 0.83 to 0.98) was also found to be associated with the use of antiplatelet agents compared to no active intervention.[112] There remains ongoing debate regarding the potential utility of low-dose aspirin for prevention of pre-eclampsia in low-risk pregnant women.[113] Although evidence for the optimal time to commence aspirin prophylaxis, and the optimal dose are not available, national UK guidance recommends 75mg/day is prescribed from 12 weeks' gestation (as this was the gestation that treatment was commenced in most of the trials).[16]

Other dietary supplements have been trialled for prevention of pre-eclampsia including calcium[114] and vitamins such as C and E[115], but the evidence for routine use of these supplements is lacking. There are ongoing trials assessing other supplements including folic acid. Initial data suggested that a significant risk reduction in the incidence of pre-eclampsia with high dose folic acid 4mg/day (adjusted odds ratio 0.37, 95% confidence interval 0.18 to 0.75).[116] However, these data were from an initial cohort study, and the results from the subsequent multicentred international Folic Acid randomised Controlled Trial (FACT) that has recently completed recruitment, are awaited.[117]

1.3.4 Fetal monitoring

The increased risk of fetal growth restriction, hypoxia and intrauterine death in pregnancy complicated by chronic hypertension has been established.[8] Data regarding optimal fetal monitoring by ultrasound from cohorts of women with chronic hypertension are limited.[16] Uterine artery Doppler flow velocity waveforms are commonly measured around 20 weeks' gestation, as raised mean pulsatility index (or resistance index) is associated with an increased

risk of subsequent fetal growth restriction and superimposed pre-eclampsia.[118,119] Assigning level of risk can in turn guide frequency of subsequent longitudinal assessment of fetal biometry, liquor volume and fetal Doppler assessment, but the evidence for this management strategy is limited.[16] National guidance currently recommends routine fetal biometry, liquor volume and fetal Doppler assessment around 28 weeks and 34 weeks' gestation in pregnancy complicated by chronic hypertension. This should allow timely detection of fetal growth restriction secondary to the maternal condition and inform subsequent antenatal management.

The routine use of cardiotocography for antenatal monitoring of fetal wellbeing in pregnant women with chronic hypertension is not recommended. However, routine cardiotocography during labour is recommended in UK intrapartum care guidance[120] and healthcare professionals should be vigilant for abnormal fetal heart rate patterns and the increased risk of placental abruption in this group.[43]

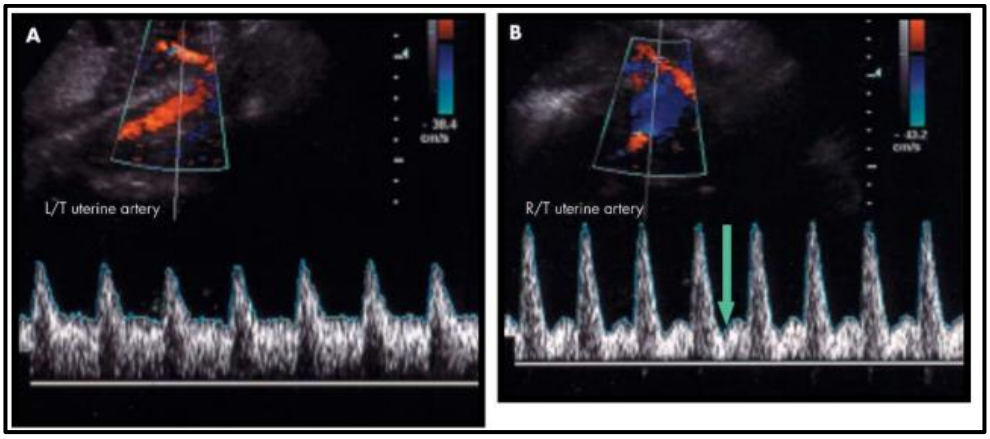


Figure 1.12 Doppler uterine artery assessment showing (A) normal flow velocity waveform with low resistance, and (B) abnormal flow velocity waveform with an early diastolic notch (arrow) and a high resistance index (James and colleague 2004)[23]

1.3.5 The challenges of measuring blood pressure in pregnancy

Accurate measurement of blood pressure in pregnancy is vital for diagnosis and safe management of chronic hypertension in pregnancy.[121] National antenatal care guidelines highlight factors to be considered by all healthcare professionals when measuring blood pressure in pregnancy.[22] These include: the use of a correctly sized inflation cuff, inflation of the cuff to 20-30 mmHg above the palpable systolic blood pressure, deflation of the cuff at a

rate of 2 mmHg per second, recording the blood pressure to the nearest 2 mmHg and use of Korotkoff V (disappearance of the sound) to indicate diastolic blood pressure.

In practice many of these recommendations are not adhered to. Studies both in and outside pregnancy have identified the phenomenon of 'terminal digit preference' with healthcare professionals of all clinical backgrounds rounding blood pressure measures to the nearest 10 mmHg.[122,123] The incorrect selection of inflation cuff size is also commonly reported.[121] If the arm circumference is greater than 33 cm a large cuff is mandated or the blood pressure recorded will be falsely elevated and therefore inaccurate.[124] Pregnancy is associated with variable weight gain and consideration of arm circumference should be made at each antenatal assessment.

Automated blood pressure devices may overcome much of the interobserver variation in blood pressure measurement described above, however, due to the physiological changes in maternal vasculature associated with pregnancy, individual machines require validation for use in pregnancy.[125] Automated blood pressure devices that are not validated for use in pregnancy underestimate blood pressure in pre-eclampsia.[126] This is thought to relate to decreased vascular compliance and increased interstitial oedema associated with pre-eclampsia.[127]

In view of the importance of accurate blood pressure measurement in women with chronic hypertension in pregnancy, it is vital that clinicians caring for women with this condition are able to measure blood pressure correctly. Healthcare professionals should be aware of the advantages and disadvantages of the blood pressure devices available for use in pregnancy and feel able to raise concern regarding devices inaccurate for use in pregnancy or poor technique observed.

1.3.6 Treatment initiation and therapeutic blood pressure targets

Internationally, guidelines vary regarding the threshold above which hypertension should be treated in pregnancy.[14] The UK guideline for the treatment of hypertension in pregnancy recommends that pregnant women with hypertension (gestational or primary chronic hypertension) should be prescribed antihypertensive treatment if blood pressure exceeds 150/100 mmHg.[16] The American College of Obstetricians and Gynaecologists recommends

utilising antihypertensive treatment to control chronic hypertension in pregnancy if blood pressure exceeds 160/105 mmHg.[128]

Once treatment is initiated, guidance for therapeutic blood pressure targets also varies.[14] There is evidence that control of blood pressure in pregnancy needs to be carefully balanced. Persistent severe hypertension causes end organ damage to the mother, but lowering the blood pressure too far is postulated to reduce placental blood flow and in turn increase the risk of fetal growth restriction.[129,130] The Control of Hypertension In Pregnancy Study (CHIPS) randomised women with hypertension in pregnancy to 'tight' (target diastolic blood pressure 85 mmHg) or 'less tight' control (target diastolic blood pressure 100 mmHg).[15] Magee and colleagues (2015) reported that 'tight' control (versus 'less tight' control) did not impact the primary composite perinatal outcome of pregnancy loss and high-level neonatal care within the first 48 hours of infant life (31.4% versus 30.7%) or the overall risk of small for gestational age infants (birthweight <10th centile) 'tight' control 16.1% versus 'less tight' control 19.7% (odds ratio 0.78, 95% confidence interval 0.56 to 1.08). Subgroup analyses of those with chronic hypertension suggested a possible trend towards small for gestational age birthweight <10th centile (13.9% versus 19.7%; adjusted odds ratio 0.66, 95% confidence interval 0.44 to 1.00), however it was notable that in this subgroup the primary perinatal outcome was no different (odds ratio 1.08, 95% confidence interval 0.78 to 1.51). The frequency of severe hypertension was significantly higher with less-tight control (40.6% versus 27.5%; odds ratio 1.8, 95% confidence interval 1.3 to 2.4).[15] There are likely to be additional benefits of reducing the incidence of severe hypertension through a decrease in short and long-term maternal morbidity and mortality from stroke and other end-organ damage,[49,62,131-133] and potential cost savings with a reduction in healthcare resource use.[134,135]

1.3.7 Timing of birth

The timing of birth will depend on the maternal and fetal condition during pregnancy. If complications such as superimposed pre-eclampsia or fetal growth restriction develop, delivery may be expedited. However if the maternal condition is stable, and fetal biometry, liquor volume and Dopplers are normal, there are limited data in women with chronic hypertension to guide timing of birth once 37 weeks' gestation is reached.[16] The HYPITAT study (2009) reported findings from 756 women with gestational hypertension or mild pre-eclampsia and singleton pregnancies enrolled at 36 to 41 weeks' gestation, who were randomly assigned to immediate delivery (within 24 hours) versus expectant management.[136] There was a

significant reduction in the primary composite maternal adverse outcome (maternal mortality, eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease, placental abruption, progression to severe hypertension or proteinuria, and major post-partum haemorrhage): 31% in the immediate delivery group versus 44% in the expectant management group (relative risk 0.71, 95% confidence interval 0.59 to 0.86). There were no differences in perinatal outcomes. Although Koopmans and colleagues did not enrol women with chronic hypertension, the findings of this study have been applied to national guidance and it is recommended that clinicians consider offering initiation of delivery from 37 weeks' gestation following discussion of the potential risks and benefits with the individual woman and her partner.[16]

The HYPITAT- II trial (2015) compared immediate birth versus expectant management in 897 women with hypertensive disorders of pregnancy between 34 and 37 weeks' gestation.[137] Broekhuijsen and colleagues found a small decrease in the composite adverse maternal outcome in those randomised to immediate birth versus those managed expectantly (1.1% versus 3.1%; relative risk 0.36, 95% confidence interval 0.12 to 1.11), but a significant increase in neonatal respiratory distress syndrome associated with immediate delivery versus expectant management (5.7% versus 1.7%; relative risk 3.3, 95% confidence interval 1.4 to 8.2).[137] The authors concluded that 'for women with non-severe hypertensive disorders at 34 to 37 weeks' gestation, immediate delivery might reduce the already small risk of adverse maternal outcomes, but it significantly increases the risk of neonatal respiratory distress syndrome, therefore, routine immediate delivery does not seem justified'. A limitation of this study was the inclusion of a heterogeneous group of women with hypertensive disorders of pregnancy. Pre-eclampsia is associated with a greater risk of adverse outcomes than gestational hypertension.[138,139] The maternal and perinatal risks and benefits of immediate birth versus expectant management between 34 and 37 weeks' gestation in women with pre-eclampsia is currently being examined in the PHOENIX trial (Pre-eclampsia in HOspital: Early iNductIon or eXpectant management: http://www.isrctn.com/ISRCTN01879376). The optimal timing of delivery in women with chronic hypertension warrants further investigation.

1.3.8 Postnatal considerations

National UK guidance for the management of women with hypertensive disorders recommends a minimum of daily maternal blood pressure monitoring for the first two days after birth, with a further blood pressure assessment between three to five days postpartum,

when blood pressure often increases.[16] Additional monitoring during the postnatal period and prior to the six-week check with the woman's primary care physicians will depend on blood pressure control and the complications that have arisen during the pregnancy, such as superimposed pre-eclampsia.[16] Ideally the antihypertensive agent regime used during the pregnancy should be continued in the immediate postpartum period, but if methyldopa has been prescribed, cessation and initiation of a different agent is recommended within two days of birth due to the risk of postpartum depression.[16] Antihypertensive agents that have no known adverse effects on breastfed infants include: labetalol, nifedipine, enalapril, captopril, atenolol, and metoprolol.[16] Choice of agent will depend on pre-pregnancy treatment and the existence on other underlying pathology; for example, enalapril may be preferentially considered for women with chronic kidney disease.[23] The target blood pressure is <140/90 mmHg as per UK guidance for the management of hypertension outside pregnancy.[1] The minimum standard of care required at the six-week postnatal review should include blood pressure measurement, urinanalysis to check for proteinuria and review of long term antihypertensive treatment.[16]

The importance of postnatal follow-up is highlighted in a study conducted by Cirillo and colleagues (2015) which examined the relationship between pregnancy complications and cardiovascular disease or death in a 50-year follow-up of the Child Health and Development Studies pregnancy cohort.[140] Their study included 14,062 women and found that pre-existing hypertension was associated with a hazard ratio of 3.5 (95% confidence interval 2.4 to 5.1) of death from cardiovascular disease compared to women without pre-existing hypertension and that if women with pre-existing hypertension developed superimposed pre-eclampsia, the risk of death increased further (hazard ratio 5.6; 95% confidence interval 2.09 to 15.18).[140]

Pregnancy offers a unique opportunity to educate and empower women with chronic hypertension, in addition to optimising treatment and improving understanding of the impact of their disorder on their future health.

1.4 Antihypertensive treatment

Choice of antihypertensive agent in pregnancy is restricted by potential teratogenicity. Robust safety data for each class of drugs, as well as individual agents, are limited. Antihypertensive agents commonly used in pregnancy include labetalol (combined alpha and beta-blocker), nifedipine (calcium channel blocker) and methyldopa (centrally acting agent).[141] A population

study conducted by Cea and colleagues (2014) reported antihypertensive prescribing patterns captured by The Health Improvement Network (THIN) primary care database in 1995 women with chronic hypertension who were pregnant between 1996 and 2010.[31] Only 36% of this cohort were prescribed antihypertensive treatment in the three months prior to pregnancy and the most common antihypertensive agents were diuretics (11%), beta-blockers (10%) and ACE inhibitors (10%). The most commonly prescribed antihypertensive agents in pregnancy were methyldopa and labetalol. This study was limited by the lack of secondary care data; high risk pregnancies, such as those complicated by chronic hypertension, are frequently cared for exclusively by obstetricians in secondary or tertiary care settings.

Another population study conducted on the Medicaid beneficiaries in the USA by Bateman and colleagues (2012), examined the antihypertensive agent prescriptions in pregnancies between 2000 to 2007.[142] They found that in the three months prior to pregnancy, the most common medication classes were beta blockers, thiazides, ACE inhibitors, dihydropyridines (sub-group of calcium channel blockers), and central alpha antagonists. These agents were also the most common classes of exposure during the first trimester (though the proportion prescribed central alpha antagonists such as methyldopa, was much greater). In the second trimester, the proportion of women prescribed ACE inhibitors and thiazides had markedly reduced, and the proportion exposed to central alpha antagonists (methyldopa 42%), alpha beta blockers (labetalol 15%), and dihydropyridines (nifedipine 20%) increased. The most commonly prescribed agents in the third trimester were similar to those used in the second. The limitations of this study include the lack of detail regarding which agents were prescribed for which condition, and the assumption that all antihypertensive agents were being prescribed as blood pressure lowering treatment. Nifedipine can be prescribed in the third trimester off-licence as a tocolytic and this is likely to have contributed to the substantial increase in the proportion of women prescribed dihydropyridines in the third trimester.

The challenge of assessing the risk of teratogenicity of antihypertensive agents is increased due to the impact of the disease process itself on the risk of congenital malformations. Bateman and colleagues conducted a matched case-control study comparing data collected from a Medicaid cohort (878,126 women) and compared normotensive controls with women with treated and untreated chronic hypertension to compare the risk of congenital malformations.[143] Pregnancies complicated by treated chronic hypertension compared to normotensive controls were at increased risk of congenital malformations (odds ratio 1.3, 95%

confidence interval 1.2 to 1.5); however pregnancies with untreated chronic hypertension compared with normotensive controls were also at increased risk (odds ratio 1.2, 95% confidence interval 1.1 to 1.3). The analysis of organ-specific malformations revealed that treated and untreated chronic hypertension was associated with a significant increase in the risk of cardiac malformations (odds ratio 1.6, 95% confidence interval 1.4 to 1.9 and odds ratio 1.5, 95% confidence interval 1.3 to 1.7 respectively).[143]

1.4.1 Labetalol

Pharmacodynamics

Labetalol is a racemate with alpha and non-selective beta adrenoceptor antagonist activity. Two of the four isomers contained within the clinical preparation are active, causing non-selective competitive beta-1 and beta-2 receptor blockade, selective competitive blockade of post synaptic alpha-1 receptors, and partial agonist activity at the beta-2 receptors.[144] Labetalol is between three and seven times more potent for beta blockade than alpha blockade, an effect that is most apparent at low oral doses and when given intravenously.[145,146] Blood pressure is lowered partially through alpha blockade causing decreased peripheral vascular resistance and therefore vasodilation, activation of the beta-2 adrenoreceptors on the vascular smooth muscle, and beta-1 adrenoceptor blockade preventing reflex sympathetic stimulation of heart rate and cardiac output, and reducing renal renin secretion.[146,147]

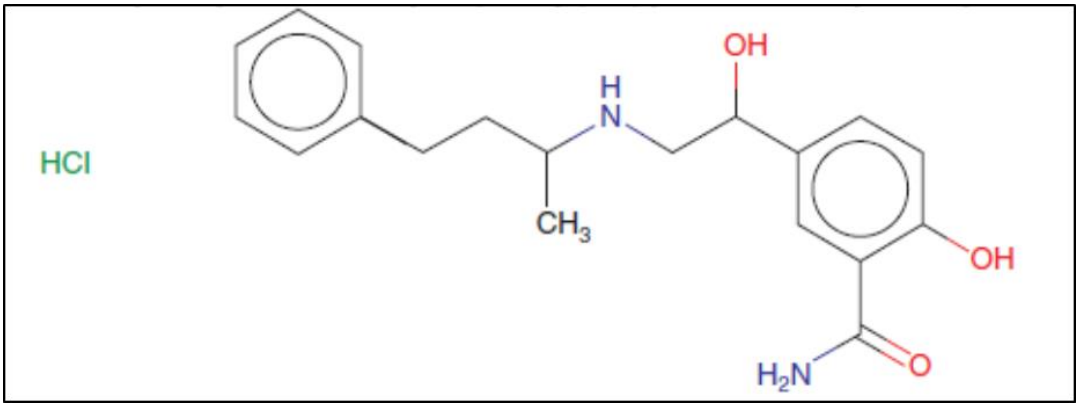


Figure 1.13 Chemical structure of labetalol (5-(1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl) salicylamide)(Magee and colleagues, 2015)[144]

Pharmacokinetics

Labetalol has extensive first-pass hepatic metabolism and demonstrates increased bioavailability when taken with food.[148] Peak plasma concentrations usually occur two hours after oral ingestion and maximal blood pressure lowering effect is noted one to four hours post ingestion.[144] Approximately 60% of the drug is renally excreted.[148] It has a short half-life (4

to 6 hours), requiring dosing to be split to two to three times per day, which can contribute to difficulties with adherence. A recent study examining the impact of gestation on the pharmacokinetics of labetalol by Fisher and colleagues (2014) found a significant increase in the oral clearance rate across gestation and when compared to the oral clearance rate outside pregnancy.[149] Possible side-effects include drowsiness, weakness, and somnolence, and it is relatively contraindicated in women with asthma as it can cause bronchospasm.

Safety

The fetal risks of labetalol appear to be low.[144,150,151] Labetalol is the only antihypertensive agent that holds a Medicines and Healthcare Regulatory Agency (MHRA) licence for use in pregnancy, but this is primarily a reflection of the difficulties surrounding licensing drugs for use in pregnancy.[152] In spite of this the manufacturers of labetalol still advise avoidance in the first trimester, which is often not feasible for women with chronic hypertension. A meta-analysis performed by Yakoob and colleagues (2013) assessed the risk of congenital malformations with the use of beta-blockers in early pregnancy and found no increased odds of all or major congenital anomalies (odds ratio 1.00, 95% confidence interval 0.91 to 1.10; 5 studies).[153] However, in the analyses examining organ-specific malformations, there was a 2.01 odds ratio of cardiovascular defects (95% confidence interval 1.18 to 3.42; 4 studies), 3.11 odds ratio of cleft lip and palate (95% confidence interval 1.79 to 5.43; 2 studies), and a 3.56 odds ratio of neural tube defects (95% confidence interval 1.19 to 10.67; 2 studies) reported, however, the independent impact of chronic hypertension on these risks was not adjusted for in this study. They concluded that 'causality was difficult to interpret given the small number of heterogeneous studies and possibility of biases'.[153] A Cochrane review of oral beta blockers for mild to moderate hypertension in pregnancy found a small increased risk of small for gestational age infants (risk ratio 1.36, 95% confidence interval 1.02 to 1.82; 12 trials, 1346 women), but raised concerns that this finding related to one outlying trial by Butters and colleagues[154].[151] They concluded that 'beta blockers are equally as safe as methyldopa' and that further evidence from large randomised controlled trials was needed to determine the optimal agent(s) and safety profile.[151] There are no convincing data from adequately powered randomised controlled trials to suggest that labetalol use is associated with fetal growth restriction, given the independent association of chronic hypertension with this risk.[8,29,144]

1.4.2 Nifedipine

Pharmacodynamics

Nifedipine is a dihydropyridine sub-type of calcium channel blocker (calcium antagonist). It primarily acts to prevent calcium ions entering at the L-type calcium channels in cardiac muscle and blood vessels, but is likely to possess some non-specific activity towards other voltage-gated calcium channels.[147] A decrease in cellular calcium results in less contraction of the vascular smooth muscle and therefore vasodilation. Nifedipine additionally causes uterine relaxation (hence its use as tocolytic agent) and bladder smooth muscle relaxation. The vasodilatation achieved with nifedipine in hypertensive women does not appear to occur in normotensive pregnant women, which explains the absence of severe hypotension induced by high doses of calcium antagonists for tocolysis in normotensive patients.[155] The ability of nifedipine to improve urine output by increasing renal blood flow and inhibiting the release of anti-diuretic hormone, in addition to reducing systemic vascular resistance, makes it a highly appropriate drug for use in hypertension in pregnancy.[147] Side-effects commonly experienced include headache, oedema, flushing, and fatigue.

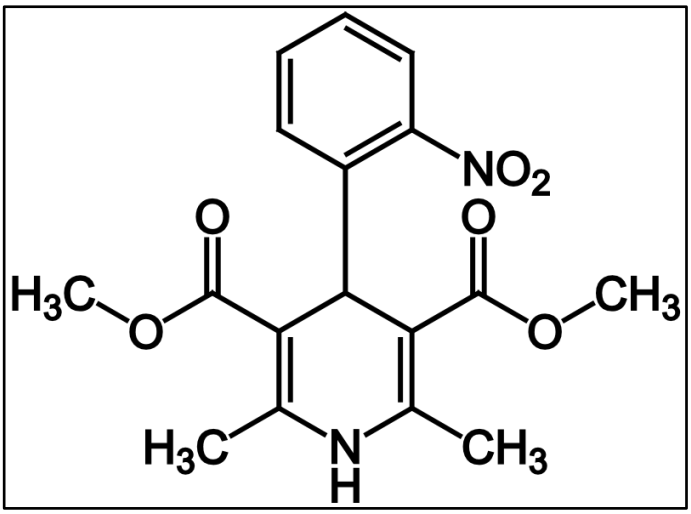


Figure 1.14 Chemical structure of nifedipine (Ayacop, 2007)[156]

Pharmacokinetics

Nifedipine is rapidly and completely absorbed by the gastrointestinal tract after oral administration. A large proportion of the drug is metabolised via the first-pass effect in the gastrointestinal wall and the liver, leaving around 60% active product with approximately 50% bioavailability.[147] The inactive metabolites are predominantly excreted by the kidneys. The elimination half-life of nifedipine depends on the formulation, but has been demonstrated outside pregnancy at 2.5 to 3.4 hours with oral capsules and 6 to 11 hours with oral tablets.[157] Peak serum concentrations after administration of 10mg of oral nifedipine have been

demonstrated at 73 ng/ml (standard deviation 17) in non-pregnant individuals.[158] Large variation in peak plasma concentrations after oral administration have been shown and are thought to be due to inter-individual variation in the first-pass effect.[159]

Prevost and colleagues (1992) studied the pharmacokinetics of oral nifedipine in 15 pregnant women with gestational hypertension.[160] They found peak serum concentrations of 39 ng/ml (standard deviation 18) occurred at approximately 40 minutes after ingestion of nifedipine 10 mg, lower and faster than in non-pregnant controls. The elimination half-life was also shorter than that demonstrated in the non-pregnant group. The authors hypothesise that these differences are partly due to the physiological changes that occur in pregnancy, but also due to increased first-pass effect.[160]

Safety

Nifedipine does not hold a licence for use before 20 weeks' gestation. This is predominantly due to animal data suggesting teratogenic risk although this increased risk has not been observed in human pregnancy. It has been suggested that since nifedipine is off patent, it is not in the financial interest of pharmaceutical companies to pursue a change in licensing. There is an inherent reluctance to give medication in pregnancy if there is any risk, but NICE state in their hypertension guideline that all antihypertensive medications have some level of risk. The need to treat the mother must be weighed against the potential risks to the fetus. This drug is used widely both nationally and internationally for treatment of chronic hypertension throughout pregnancy and, in what follows, the argument for its use as a first-line treatment option from 12 weeks' gestation are reviewed.

There are theoretical concerns about use of calcium-channel blockers in early pregnancy. Many of the processes of embryogenesis appear to be calcium-dependent in animals and are thought to be blocked by calcium antagonists. Such processes include development of the somites, optic cup formation, and possibly organization of the morula. Teratology studies in rabbits have shown an increase in digital defects in the offspring of female rabbits treated with nifedipine.[161,162] These defects consisted of reduction, absence, or malformation of the distal phalanges, associated with abnormal cartilage differentiation and ossification. It is believed that the abnormalities were secondary to decreased uteroplacental blood flow rather than a direct effect of the drug on the phalanges; however, experiments in rats suggest that hyperphalangism produced in the offspring by maternal nifedipine may be due to effects on

calcium channels of the limb bud mesenchymal cells.[163,164] At high doses, nifedipine and other calcium channel blockers increased the incidence of cardiac defects in rats.[165] Use of nifedipine during pregnancy in sheep has also been associated with cardiovascular changes in the ewe including hypotension[166] and decreased uterine blood flow[167]. Additionally a study in late pregnant rats found high dose nifedipine (30 mg/kg/day) to be associated with vasodilatation in the uterus and in the placenta and some decrease in pup weight, but no adverse effects on pup survival.[168] Human studies have not reproduced these findings.

These animal studies are flawed in two ways. Firstly, none of these animals were hypertensive, so the large doses of nifedipine they were given caused relative hypotension, which is known to have an adverse effect on the developing fetus by decreasing uteroplacental blood flow and secondly, the animal species have significant pharmacokinetic or pharmacodynamic differences to humans. For example, it was not understood why cleft palate followed gestational exposure to corticosteroids in animals but not in humans until it was shown that these drugs mediate their effect through a receptor that does not exist in the human embryonic palate.[169] This highlights the importance of understanding the mechanism by which drugs cause defects before extrapolating data from animal studies to human pregnancy. Scott and colleagues (1997) concluded in one of their animal studies 'we interpret these results to indicate that high dosage of calcium channel blockers during rat embryogenesis leads to a low incidence of cardiovascular malformation and an increase of anatomic variants. It is impossible at this time to decide whether these adverse outcomes are indirect, resulting from the toxicity to maternal cardiovascular function or a direct effect on calcium homeostasis in the embryo. Nevertheless, at therapeutic doses where maternal toxicity is minimal these agents should pose little hazard for the mammalian embryo'.[165]

An analysis of all reports submitted to the US FDA of congenital defects in pregnancies involving nifedipine between 1981 and 2000 identified 15 that included congenital defects,[170] but these case reports cannot be used to establish causation. A randomised clinical trial conducted by Bortolus (2000), found no significant increase in the frequency of congenital anomalies, small size, or developmental delay in 94 eighteen-month old children whose mothers were treated with nifedipine for hypertension between 12 and 34 weeks gestation.[171] The successful use of nifedipine to control hypertension in severe pre-eclampsia has also been reported with no harmful fetal effects.[172-176] Parazzini and colleagues (1998) randomised 145 pregnant women with chronic hypertension between 12 to 34 weeks' gestation to nifedipine

or no treatment for control of their blood pressure. They reported congenital anomalies in both treatment and the control group and found no significant increase with nifedipine.[177] Magee and colleagues also published a multicentre cohort study in 1996 examining the safety of calcium-channel blockers in the first trimester of pregnancy and found no increase in major malformations within the 78 cases studied.[178] They concluded calcium-channel blockers do not represent a major teratogenic risk, although it is recognised that teratogenicity studies may need to be considerably larger to reach this conclusion safely. Weber-Schoendorfer and colleagues (2008) conducted a multicentre prospective observational study of the European Network of Teratology Information Services (ENTIS), comparing the major birth defect rates between a cohort of pregnant women exposed to calcium channel blockers during the first trimester (n = 299) and a control group not exposed to potential teratogens (n = 806). The results demonstrated that major birth defects were no more common in the study group than in the control group.[179]

1.4.3 Methyldopa and other antihypertensive agents

Methyldopa is a methyl-substituted amino acid that acts as a precursor for methylated catecholamine analogues which compete with catecholamines in the nervous system.[180,181] The antihypertensive effect is mediated by an accumulation of methylated catecholamine analogues in vasoactive centres of the central nervous system, which interferes with the effect and synthesis of noradrenaline and other active catecholamines.[182] Methyldopa is incompletely absorbed from the gastrointestinal tract. Bioavailability is estimated at 25% (interquartile range 8 to 62%) and maximum plasma concentrations after a single 500mg oral dose have been demonstrated from 0.95 to 2.8 mg/ml, occurring 2 and 4 hours after administration.[182]

The safety of methyldopa has been assessed in a randomised controlled trial of 242 participants for the treatment of hypertension in pregnancy in the 1970s.[183] The infants born to the mothers that took part in this study were followed-up until they were seven years old with no adverse effects demonstrated.[184] However, in the postnatal period, national UK guidance recommends cessation of this treatment immediately following delivery due to risk of depression.[16] Depression and somnolence are also evident during pregnancy and some clinicians question if methyldopa should be a first line agent antenatally. This agent has not been studied in the work presented in this thesis.

ACE inhibitors are contraindicated in the second and third trimester as in-utero exposure is associated with oligohydramnios, intrauterine growth restriction, hypocalvaria, renal dysplasia and stillbirth.[185,186] There are differing opinions on the use of these agents in the first trimester due to concerns regarding an associated increased risk of congenital malformations;[187] however, some studies suggest the increased risk seen is likely to relate to the condition itself rather than this agent.[143,188] Similarly, avoidance of ARBs is also recommended based on concerns for congenital malformations.[189]

Table 1.1 Safety data for antihypertensive drugs in pregnancy (derived from data presented in the NICE 'Hypertension in pregnancy' guideline)[16]

Agent	Safety summary
Centrally acting	
Methyldopa	Mild hypotension in babies in first 2 days of life, but no obvious association with congenital abnormalities.
Beta-blockers	
Labetalol	Rare mild hypotension in first 24 hours of life and very rare hypoglycaemia have been reported. No obvious association with congenital abnormalities has been demonstrated.
Atenolol	Low birthweight and placental weight have been demonstrated. Decreased fetal heart rate has also been described, but no obvious association with congenital abnormalities has been reported.
Metoprolol	No association with congenital abnormalities has been reported.
Oxprenolol	No association with congenital abnormalities has been reported.
Pindolol	No association with congenital abnormalities has been reported.
Calcium channel blockers	
Nifedipine	No association with congenital abnormalities has been reported in humans.
Amlodipine	No reports available.
Verapamil	No association with congenital abnormalities has been demonstrated.
Alpha-blockers	
Doxazocin	No known association with congenital abnormalities.
Prazosin	No known association with congenital abnormalities.
Diuretics	
Chlorothiazide	Possible association with congenital abnormalities and additionally, possible neonatal thrombocytopaenia, hypoglycaemia and hypovolaemia, and electrolyte imbalances
Bendroflumethiazide	No adverse fetal effects reported, but maternal hypovolaemia evident.
Furosemide	No obvious fetal or neonatal effects.

1.5 Placental, endothelial and renal biomarkers in hypertensive disorders of pregnancy

Despite decades of research, the prediction and diagnosis of superimposed pre-eclampsia and fetal growth restriction remain a challenge. Identifying the women at greatest risk would aid stratification of antenatal care pathways and target utilisation of additional resources such as fetal ultrasound surveillance. The discovery of biomarkers associated with adverse outcomes in women with chronic hypertension would also facilitate recruitment to trials of potential

therapeutic agents, improve the accuracy of diagnosis, and allow timely intervention whenever complications develop.[190]

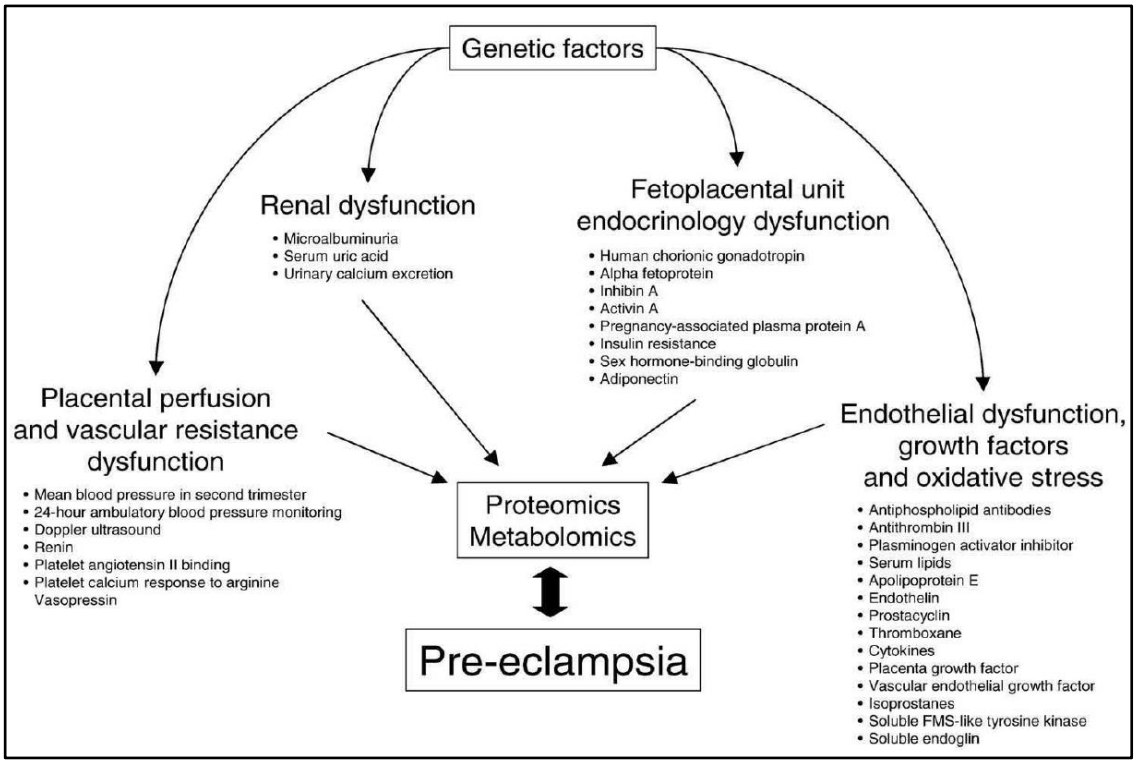


Figure 1.15 Biomarkers of pre-eclampsia grouped into four major categories (Carty and colleagues, 2008)[190]

Within this chapter, the potential utility of biomarkers within the categories of placental dysfunction (Placental growth factor), endothelial dysfunction (Syndecan-1), and renal dysfunction (renin, aldosterone, angiotensinogen: creatinine ratio, protein: creatinine ratio and albumin: creatinine ratio) are considered.

1.5.1 Placental growth factor

Placental growth factor (PlGF) is a dimeric glycoprotein and member of the vascular endothelial growth factor (VEGF) family of proangiogenic growth factors.[191] The human *plgf* gene has been mapped to chromosome 14q24.[192] PlGF is expressed predominantly in the placenta across gestation and is suggested to regulate trophoblast growth and differentiation.[192,193] PlGF is also thought to be involved in the invasion of the trophoblasts into the maternal decidua.[194] It is capable of inducing proliferation, migration, and activation of endothelial cells. PlGF is additionally expressed at low concentrations in other organs including the heart, lung, thyroid, skeletal muscle, and adipose tissue under normal physiological conditions.[195-197]

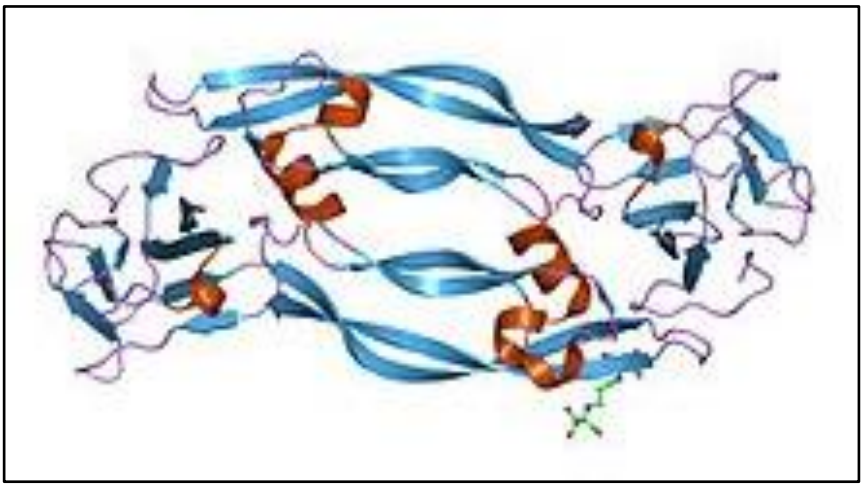
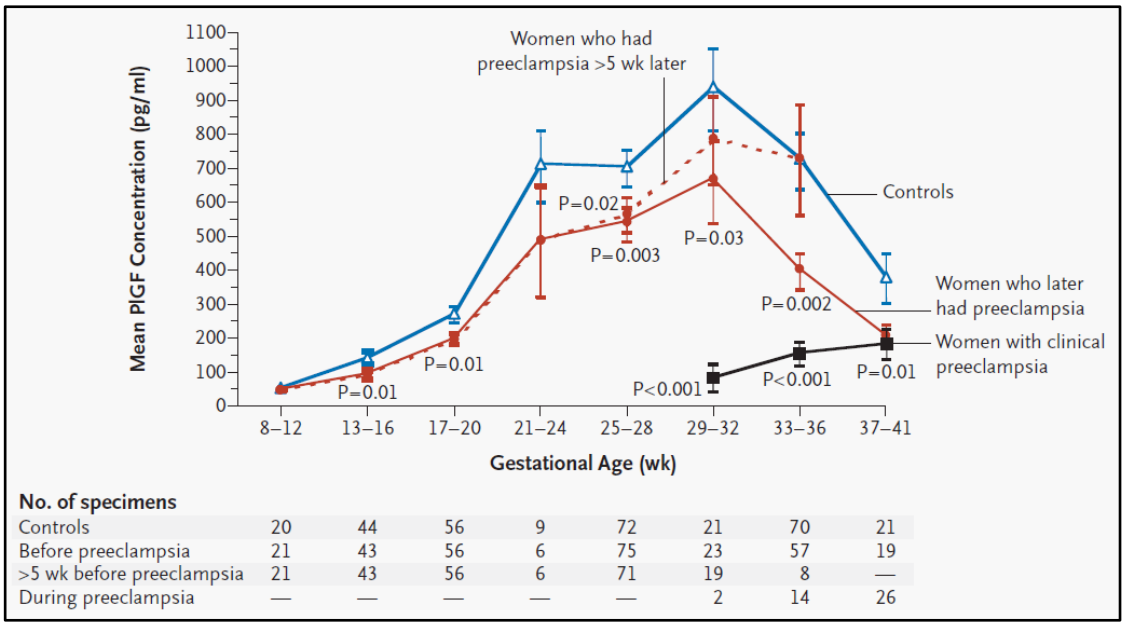


Figure 1.16 The chemical structure of placental growth factor (Christinger and colleagues, 2004)[198]

The role of PlGF in the pathogenesis of pre-eclampsia has been the focus of more recent research in this field. Reduced concentrations of circulating PlGF have been observed in women with pre-eclampsia in association with increased concentrations of sFlt-1 (an anti-angiogenic protein). It is hypothesised that s-Flt-1 binds to the PlGF receptor binding domain, which in turn prevents PlGF interacting with the endothelial receptors on cell surfaces and induces endothelial dysfunction.[199,200] Chappell and colleagues (2002) conducted a cohort study examining the relationship between longitudinal concentrations of biomarkers of placental and endothelial dysfunction and subsequent diagnosis of pre-eclampsia.[200] They demonstrated that lower concentrations of PlGF at 20 and 24 weeks' gestation in the women who subsequently developed pre-eclampsia, compared to those who did not, were predictive of subsequent diagnosis of pre-eclampsia (ROC area 0.85; 95% CI 0.71- 0.99 versus low risk controls, at 24 weeks' gestation).[200] Subsequently, Levine and colleagues (2004) confirmed these findings in a nested case-control study in 120 pregnant women, 60 with subsequent pre-eclampsia and 60 who remained normotensive throughout pregnancy.[199] They demonstrated a gestational rise in PlGF concentrations with a peak at 26 to 30 weeks and then a decline towards term. The PlGF concentrations across gestation were significantly lower in the women who developed pre-eclampsia compared to those who did not.[199]



No. of specimens								
Controls	20	44	56	9	72	21	70	21
Before preeclampsia	21	43	56	6	75	23	57	19
>5 wk before preeclampsia	21	43	56	6	71	19	8	—
During preeclampsia	—	—	—	—	—	2	14	26

Figure 1.17 Levine and colleagues (2014): Mean concentration of placental growth factor across gestation in pregnant women who did and did not develop pre-eclampsia[199]

Data from this work, and another follow-up study from this group, demonstrated that prior to the onset of clinical signs or symptoms of pre-eclampsia, lower concentrations of circulating PlGF were detected.[199,201] A case-control multicentre study reported by Verlohren and colleagues (2010), demonstrated that mean serum sFlt-1/PlGF ratios in patients with pre-eclampsia were significantly higher than that of women in the control group (354.5 ± 44.84 versus 19.43 ± 1.62, respectively; $P < 0.0001$) and that the sFlt-1/PlGF ratios related to disease severity, thus offering a potential aid in the management of pre-eclampsia.[202] This study was unable to determine which of these biomarkers provided the optimal tool in the diagnosis and management of pre-eclampsia.

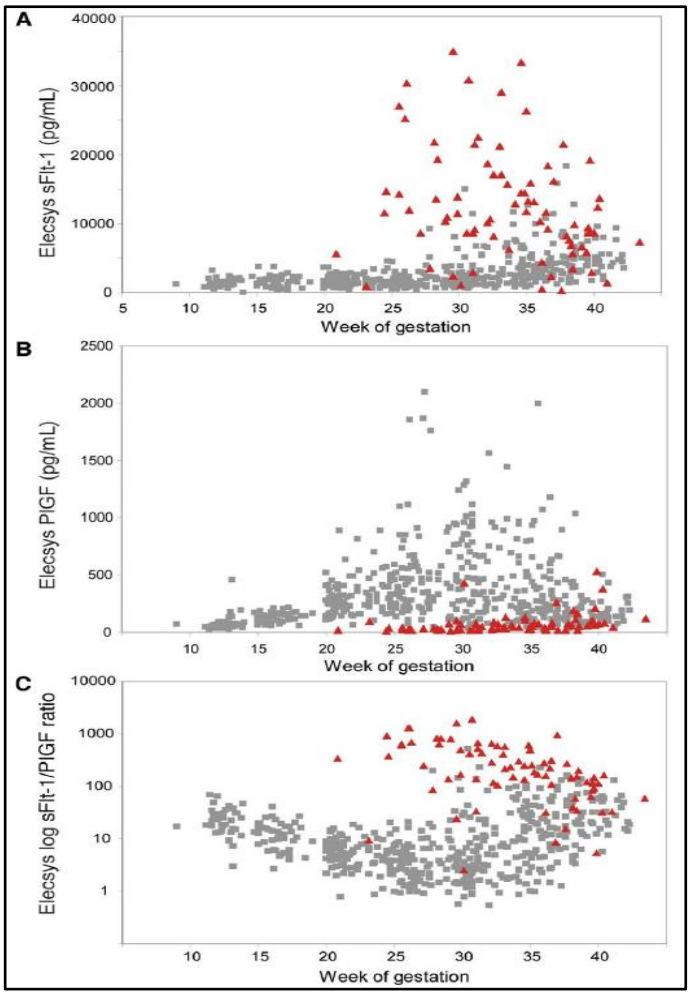


Figure 1.18 Verlohren and colleagues (2010): Maternal serum levels of sFlt-1, PlGF, and sFlt-1/PlGF ratio in pre-eclampsia versus controls[202]

*Scatterplots of maternal serum concentrations of **A**, soluble fms-like tyrosine kinase (sFlt)-1; **B**, placental growth factor (PlGF); and **C**, calculated sFlt-1/PlGF ratio of preeclamptic (PE) versus gestational age-matched control patients. Red triangles represent serum values of sFlt, PlGF, and calculated sFlt-1/PlGF ratio of PE pregnancies. Grey dots represent control patients.*

The PELICAN study, reported by Chappell and colleagues (2013), examined the diagnostic accuracy of low plasma PlGF concentrations (<5th centile for gestation) in women presenting with suspected pre-eclampsia between 20 and 35 weeks' gestation.[203] In women enrolled before 35 weeks' gestation (n=287). PlGF <5th centile had high sensitivity (0.96; 95% confidence interval, 0.89 to 0.99) and negative predictive value (0.98; 95% confidence interval 0.93 to 0.995) for confirmed pre-eclampsia requiring delivery within 14 days.[203] In addition the area under the receiver operating characteristic curve for low PlGF (0.87, standard error 0.03) for predicting pre-eclampsia requiring delivery within 14 days was greater than all other tests commonly used in the diagnosis and management of pre-eclampsia in women presenting with suspected preeclampsia.[203]

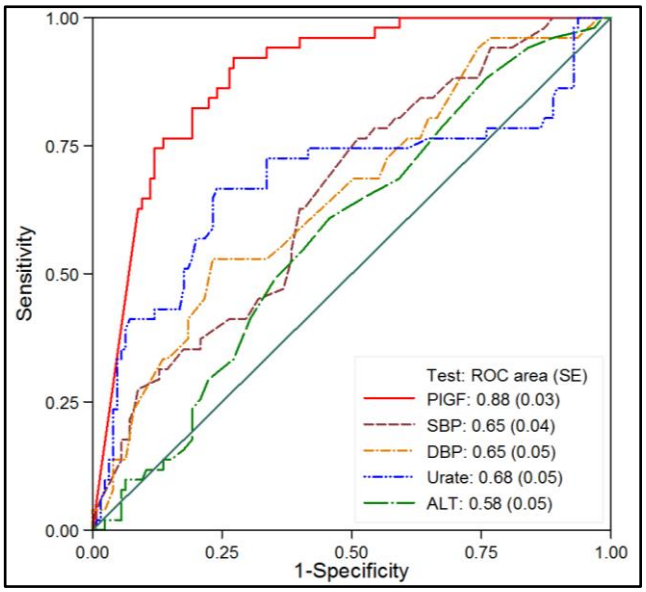


Figure 1.19 Chappell and colleagues (2013): Receiver operator characteristics areas (standard error) for PlGF compared with five other tests (systolic and diastolic blood pressure, uric acid, and alanine transaminase) in determining pre-eclampsia requiring delivery within 14 days[203]

Analysis includes 176 women presenting before 35^{+0} weeks' gestation with all tests measured using routine parameters. ALT indicates alanine transaminase; DBP, diastolic blood pressure; PlGF, placental growth factor; and SBP, systolic blood pressure.

The utility of PlGF in the diagnosis of superimposed pre-eclampsia has also been explored by Bramham and colleagues (2016), who measured longitudinal and time-of-disease PlGF concentrations in a cohort of women with chronic hypertension and/or chronic kidney disease.[204] Lower values of plasma PlGF (less than the fifth centile) were associated with a diagnosis of superimposed pre-eclampsia requiring delivery within 14 days when assessed between 20^{+0} and 36^{+6} weeks' gestation (receiver operating characteristic 0.85; standard error 0.06). This is particularly important given the challenges of diagnosing superimposed pre-eclampsia in women with underlying hypertension and proteinuria.

1.5.2 Syndecan-1

The syndecans are a group of cell surface heparan sulphate proteoglycans.[205] Syndecans are expressed on the surface of all adherent cells and on many non-adherent cells. They are transmembrane proteins with an extracellular domain where heparan sulphate chains attach to the plasma membrane with a signature transmembrane and cytoplasmic domain, which are highly homologous among the different syndecans.[205] Syndecan-1 was one of the first syndecans to be described in 1989 by Saunders and colleagues.[206] It is predominantly expressed on epithelial, endothelial and plasma cells.[207] Syndecan-1 regulates diverse cell

behaviours including adhesion, proliferation, motility, intracellular signalling, growth factor cell surface binding and angiogenesis. Syndecan-1 is strongly expressed on villus syncytiotrophoblast microvillous membranes and this expression is reduced in pre-eclampsia and fetal growth restriction compared with uncomplicated pregnancy.[208-211]

The extracellular domains of syndecan-1 are constitutively shed. The soluble form of syndecan-1 has important paracrine and autocrine functions and is a competitor for extracellular syndecan-1 growth factors and other extracellular ligands.[207,212] Syndecan-1 shedding has been described in response to wound healing with effects on inflammation, proliferation and remodelling.[213,214] Increased circulating syndecan-1 concentrations have been found in response to reactive oxygen species inflammatory stimuli such as sepsis.[213,215,216] Given the role of oxidative stress and endothelial dysfunction in the pathophysiology of pre-eclampsia, further investigation of circulating syndecan-1 in pre-eclampsia is needed.

Gandley and colleagues (2016) conducted a nested case-control study (n=44) to examine the relationship between circulating syndecan-1, gestation and subsequent diagnosis of pre-eclampsia.[207] They demonstrated that soluble circulating syndecan-1 concentrations increased significantly across gestation. They also found that syndecan-1 concentrations were significantly lower in the women who went on to develop pre-eclampsia compared to normotensive pregnant controls (174 versus 272 ng/ml; $p < 0.05$).[207] Given the small numbers in this study further investigation is required.

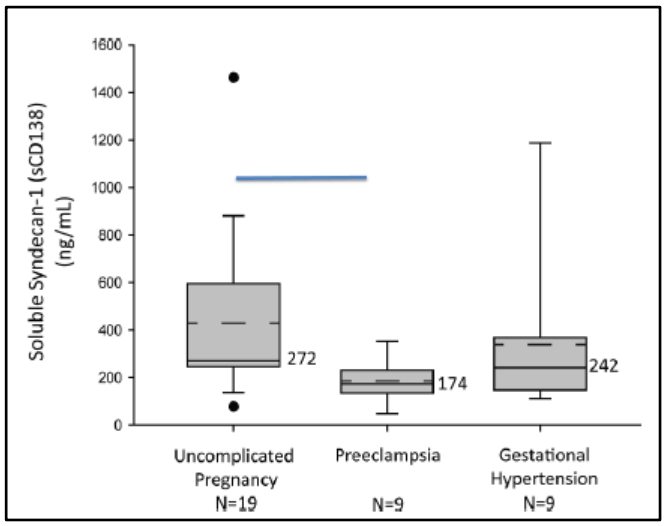


Figure 1.20 Gandley and colleagues (2016): Plasma soluble syndecan-1 is reduced at 20 weeks' gestation in women who later develop pre-eclampsia.[207]
Box-plot of syndecan-1 concentrations in mid-pregnancy by pregnancy outcome group. The solid line through the interior of each box and the accompanying numerical value correspond to the group median.

1.5.3 Renin, aldosterone and urinary angiotensinogen: creatinine ratio

The importance of the renin-angiotensin-aldosterone system (RAAS) in blood pressure homeostasis has been described in Chapter 1.2. Understanding of the changes in the RAAS that occur in pregnancy is incomplete. Variation in RAAS components in women with chronic hypertension who develop superimposed pre-eclampsia, compared to those who do not has been described previously,[109] but this study was limited by the number of participants and further investigation of the role of the systemic RAAS in the pathophysiology of superimposed pre-eclampsia is needed. The impact of ethnicity on the systemic RAAS in pregnancy complicated by chronic hypertension is yet to be investigated and may offer insight into the mechanisms underpinning disparity in maternal and perinatal outcomes associated with ethnicity.

The intrarenal renin-angiotensin system (RAS) is locally and independently active and activated in salt-sensitive rat models.[217] This has led to the hypothesis that individuals who are salt-sensitive, including those of African and Caribbean ethnicity, may have locally active intrarenal RAS, despite suppressed systemic RAAS.[218] This is of particular interest given that systemic RAAS is suppressed in salt-sensitive individuals. There are no studies examining ethnic differences in intrarenal RAS activity in chronic hypertension in pregnancy. Urinary angiotensinogen: creatinine ratio is a novel biomarker of intra-renal RAS activity.[219] Further investigation of longitudinal variation in the systemic RAAS and intrarenal RAS in women with chronic hypertension in pregnancy may provide further insight into pathophysiology.

1.5.4 Urinary protein: creatinine ratio and albumin: creatinine ratio

Proteinuria is a hallmark of pre-eclampsia, having been first described by John Lever in 1843 in association with eclampsia.[220] However, interpreting abnormal proteinuria in pregnancy remains a clinical challenge.[221] The normal physiological changes that occur in pregnancy include a 50% increase in the glomerular filtration rate, with dilatation of the renal calyces, pelvises and ureters.[93,221] Consequently, the accepted normal levels of proteinuria in pregnancy are increased to 300 mg/day, which is around double the value considered normal outside pregnancy.[221-223] An additional challenge to the evaluation of proteinuria in pregnancy complicated by chronic hypertension lies in the potential for underlying nephropathy (or other co-morbidities with associated proteinuria) in this cohort.[224]

More recently clinical practice has moved towards utilisation of the spot urinary protein: creatinine ratio and assessment of microalbuminuria via the albumin: creatinine ratio, rather than the 'gold standard' of 24-hour urine collection.[225,226] A systematic review conducted by Cote and colleagues (2008), identified nine studies including 1003 women and found spot urinary protein: creatinine ratio had a pooled sensitivity of 84% (95% confidence interval 78% to 90%), with a specificity of 76% (95% confidence interval 73% to 80%), positive likelihood ratio of 3.53 (95% confidence interval 2.83 to 4.49), and negative likelihood ratio of 0.21 (95% confidence interval 0.13 to 0.31).[225] De Silva and colleagues (2013) assessed the utility of albumin: creatinine ratio in pregnancy given that it can be assessed as a point-of-care test, and found that 48 of 160 (30%) of third trimester samples were too dilute to allow detection of urinary albumin.[226] They concluded that this made the calculation of a normal range for albumin: creatinine ratio a challenge and therefore it was less clinically useful.[226]

Poon and colleagues (2008) examined the potential of urinary albumin quantification in the prediction of pre-eclampsia between 11 and 13 weeks' gestation.[227] Their cohort study included 2679 pregnant women, 51 (1.9%) of whom developed pre-eclampsia. The median albumin: creatinine ratio in the pre-eclampsia group was higher than that in the unaffected group (0.87 mg/mmol, interquartile range 0 to 1.71 versus 0.53 mg/mmol, interquartile range 0 to 0.88; $p < 0.001$).[227] However, the authors concluded after further analysis, that albumin: creatinine ratio did not offer additional value to the prediction of pre-eclampsia when compared to other maternal variables.[227]

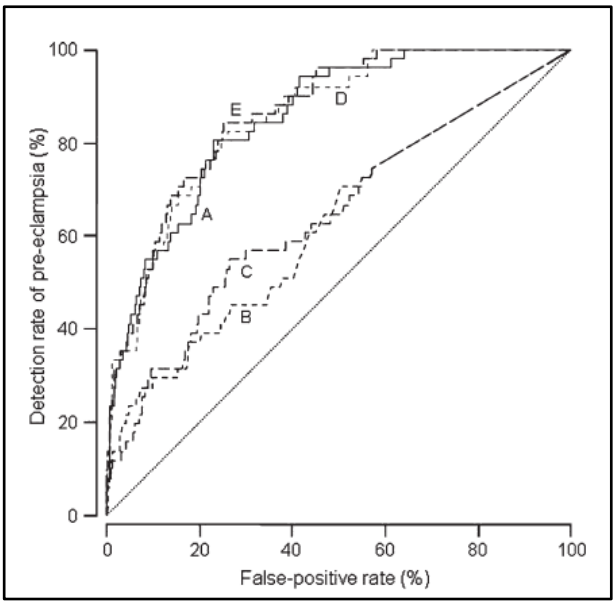


Figure 1.21 Receiver operating characteristic curve of maternal history (A), urine albumin concentration (B), urine albumin: creatinine ratio (C), the combination of history and urine albumin concentration (D) and the combination of history and albumin: creatinine ratio (E) in the prediction of pre-eclampsia (Poon and colleagues, 2008)[227]

Bramham and colleagues (2013) further investigated the relationship between proteinuria and adverse outcome performing a nested case-control study of the women who participated in the Vitamins in Pregnancy Trial.[228] They compared outcomes in pregnant women with pre-eclampsia and a 24 hour proteinuria between 300 to 499 mg/day (PE300) (n=60), with women with pre-eclampsia and a 24 hour proteinuria ≥500 mg/day (PE500) (n=161), and 725 pregnant women with either chronic or gestational hypertension but no proteinuria. They demonstrated an increase in adverse maternal and fetal outcome in the PE500 group compared with both the PE300 and non-proteinuric women, with the risk ratio of birthweight <5th centile 1.56 (95% confidence interval 1.04 to 2.33) in the PE500 group compared to the PE300 group and preterm birth before 37 weeks' gestation risk ratio 2.41 (95% confidence interval 1.56 to 3.89) in the PE500 group compared to the PE300 group.[228] They also highlighted that PE300 was associated with an increased risk of adverse maternal and fetal outcome compared with non-proteinuric pregnancy, justifying inpatient management of women with a confirmed diagnosis of pre-eclampsia. This study highlighted a relationship between proteinuria and adverse pregnancy outcome, which has been debated by other researchers.[221,228] Interestingly, and perhaps unsurprisingly, the PE500 group had higher peak serum creatinine concentrations than the PE300 group (median 75 versus 69 µmol/L; risk ratio 1.11, 95% confidence interval 1.04 to 1.19). This finding highlights the possible relationship between pre-eclampsia severity

and proteinuria. Further exploration of the utility of proteinuria assessment in pregnancy is warranted.

1.6 Non-invasive assessment of vascular function in chronic hypertension

Measures of arterial stiffness in addition to brachial blood pressure are increasingly used in the assessment of vascular function in the non-pregnant population.[229] More recently the potential utility of vascular function assessment in pregnancy has been explored.[230-232] Additional assessment of maternal vascular function may provide insight into pathophysiology and mechanism of adverse maternal and perinatal outcomes in hypertensive disorders in pregnancy and these measures may provide insight into the relationship between maternal systemic arterial stiffness and placental function.

1.6.1 The importance of vascular function assessment

Hypertension is a well-recognised cardiovascular risk factor. Arterial stiffness is affected by many factors including age,[233] hypertension,[234] diabetes mellitus,[235] atherosclerosis,[236] and end-stage renal disease.[237] In the non-pregnant general population, high systolic blood pressure, and left ventricular hypertrophy have been identified as independent risk factors for cardiovascular morbidity and mortality;[238,239] however, interest in other markers of arterial stiffness and hence assessment of individual cardiovascular risk has grown. Vascular function markers include pulse wave velocity (speed of travel of the pulse along an arterial segment), augmentation index (increase in aortic pressure after the peak of blood flow in the vessel) and central aortic pressure (the estimated peak systolic pressure in the aorta).[229]

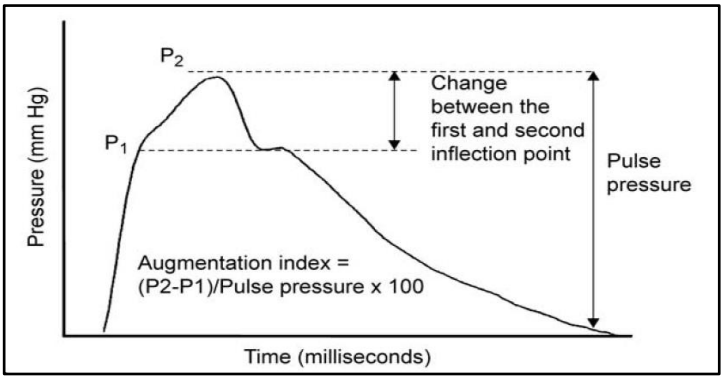


Figure 1.22 The central aortic pulse waveform represented schematically. (Khalil and colleagues, 2009)[230]
Typical ascending aortic pulse waveform, showing two systolic peaks (P1 and P2). Augmentation index is calculated as the difference between P2 and P1, expressed as percentage of pulse pressure. P1 = the first inflection point; P2 = the second inflection point

Several studies have demonstrated the independent relationship between pulse wave velocity and subsequent cardiovascular disease. Blacher and colleagues (1999) conducted a cohort study of 710 patients with chronic hypertension.[240] They measured pulse wave velocity using the Complicor Colson device which has transducers over the carotid and femoral arteries. This study demonstrated that pulse wave velocity was strongly associated with the presence of atherosclerosis and was an independent predictor of cardiovascular risk in hypertensive patients.[240] Increased pulse wave velocity in the general population has also been demonstrated as a risk factor for subsequent cardiovascular disease, independent of brachial blood pressure. Hansen and colleagues (2006) conducted age and sex-stratified sample cohort study with 1678 participants (aged 40 to 70 years) and demonstrated that pulse wave velocity predicted a composite of cardiovascular outcomes with greater performance than other cardiovascular risk factors, including 24-hour mean brachial arterial pressure.[241]

Augmentation index is regarded as an indirect marker of arterial stiffness, but a direct measure of wave reflection.[242] London and colleagues (2001) demonstrated an association between increased augmentation index and mortality in 180 cohort study participants with end stage renal disease.[243] After adjustment for confounding factors, the risk ratio for each 10% increase in augmentation index was 1.51 (95% confidence interval 1.23 to 1.86) for all-cause mortality and 1.48 (95% confidence interval 1.16 to 1.90) for cardiovascular mortality.[243]

The potential clinical utility of vascular function assessment was highlighted in the CAFÉ study reported by Williams and colleagues (2006).[244] This was a nested cohort study within the ASCOT trial, a randomised controlled trial comparing amlodipine and atenolol as treatment for chronic hypertension.[245] The CAFÉ study enrolled 2199 participants at five centres and compared vascular function parameters between antihypertensive treatment groups. They demonstrated that amlodipine use resulted in an average decrease in central aortic pressure of 4.3 mmHg (95% confidence interval 3.3 to 5.4 mmHg) compared to atenolol. Those randomised to amlodipine also demonstrated a mean 6.5% decrease (95% confidence interval 5.8 to 7.3%) in augmentation index compared to those randomised to atenolol.[244] These findings were in the absence of a significant difference in treatment effect observed in brachial blood pressure.

1.6.2 Non-invasive techniques used to assess vascular function

There are a variety of devices available to measure vascular function parameters. Pulse wave analysis is a technique that allows peripheral pressure waveforms to be recorded with subsequent generation of the corresponding central waveform, from which the pulse wave velocity, augmentation index and central aortic pressure can be derived. Pulse wave analysis is a highly reproducible technique and easy to apply.[246] It is most commonly performed on the carotid, brachial, radial or femoral arteries and can be measured using applanation tonometry, piezo-electronic method or oscillometric techniques.[242] Each device has its own merits and weaknesses, requiring internal and external validation and establishment of a normal range for each measured parameter.[229] Validation of these devices in pregnancy provides an additional challenge.

Within this thesis, pulse wave analyses were measured with the Arteriograph® (Tensiomed, Budapest, Hungary), which is an oscillometric single-cuff device. Readings were obtained from the brachial artery once an estimated aortic length and upper arm circumference had been entered into an automated computer package that programmes the device. This device has been validated against both tonometric and piezo-electronic methods for estimation of arterial stiffness parameters.[242] Unpublished work by our collaborators Cockerill and colleagues (2016), demonstrated that pulse wave velocity and augmentation index measured using the Arteriograph® in women with chronic hypertension in pregnancy had acceptable reproducibility for use in clinical practice.[247]

Figure 1.23 The Arteriograph® (Tensiomed, Budapest, Hungary)[248]

1.6.3 Assessment of vascular function in pregnancy

Vascular function measurement in pregnancy is a developing field, with potential prognostic value in hypertensive disorders.[249] A cohort study conducted by Mahendru and colleagues (2014) examined changes in pulse wave velocity, augmentation index and central aortic pressure from pre-conception, in each trimester and at four months postpartum in 54 normotensive women.[11] They demonstrated that central aortic pressure and augmentation index decrease from preconception levels during pregnancy reaching a nadir in the second trimester, and then increasing in the third trimester and returning to preconception levels by four months postpartum.[11] Pulse wave velocity does not alter from preconception levels during uncomplicated normotensive pregnancy.[11] Although this study only included a small number of women, these findings are similar to other studies examining the relationship between vascular function and normotensive pregnancy.[230,232]

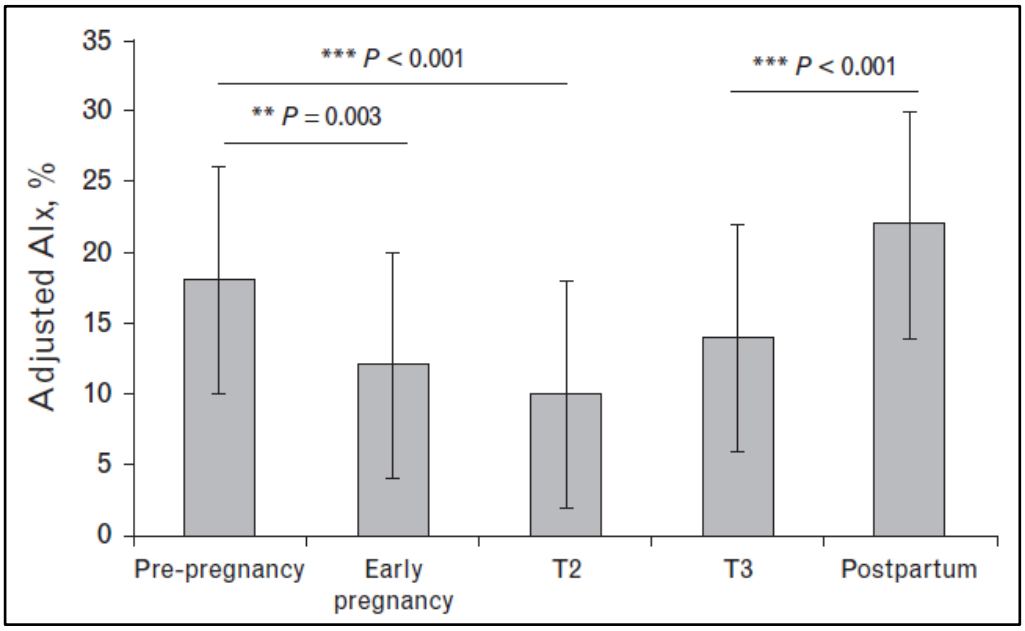


Figure 1.24 Mahendru and colleagues (2014): Changes in the augmentation index adjusted for heart rate from pre-pregnancy to the postpartum period.[11]
T2= second trimester, T3= third trimester and AIx= augmentation index

The relationship between pre-eclampsia and vascular function parameters has also been explored. Kaihura and colleagues (2009) conducted a case-control study including 69 normotensive pregnant women and 54 women with a diagnosis of pre-eclampsia, measuring vascular function at 'time-of-disease'.[250] In women with a diagnosis of pre-eclampsia, compared to the normotensive pregnant controls, all parameters were increased: pulse wave velocity (9.5 m/s (standard deviation 1.1) versus 7.5 m/s (standard deviation 1.2); p <0.0001),

augmentation index (24% (standard deviation 10) versus 4% (standard deviation 14); p <0.0001) and central aortic pressure (125 mmHg (interquartile range 120 to 134 mmHg) versus 97 mmHg (interquartile range 89 to 102 mmHg); p <0.0001) .[250] It is important to highlight that brachial blood pressure was also significantly raised in the women who developed pre-eclampsia compared to the normotensive pregnant controls. Khalil and colleagues (2009) also demonstrated that central aortic pressure and augmentation index were significantly increased in women with pre-eclampsia (n=51) compared to normotensive controls (n=80).[251] Again brachial blood pressure was also significantly increased in the women who were diagnosed with pre-eclampsia compared to normotensive pregnant controls, so the clinical utility of these tests at the time of disease is yet to be established. A more promising clinical utility of vascular function measures in predicting subsequent pre-eclampsia has been investigated. Khalil and colleagues (2014) enrolled 245 women between 11^{+0} and 13^{+6} weeks' gestation who were at high risk of developing pre-eclampsia.[252] Vascular function parameters were measured every four weeks from recruitment to delivery. Pulse wave velocity and augmentation index were significantly higher at 16 to 17 weeks' gestation in the women who were diagnosed with pre-eclampsia prior to 37 weeks' gestation compared to the normotensive group.[252] However, this study found no significant differences in the vascular function of women who developed pre-eclampsia after 37 weeks' gestation compared to normotensive pregnant controls. Further research is needed to establish if these markers offer additional sensitivity and specificity in identifying women at risk of pre-eclampsia.

There are very limited data regarding vascular function exclusively in pregnant women with chronic hypertension. A study reported by Tomimatsu and colleagues (2014) measured vascular function in 41 pregnant women with chronic hypertension between 26 and 32 weeks' gestation.[253] They found that women who developed superimposed pre-eclampsia and small for gestational age infants had higher central aortic pressure (151 mmHg (standard deviation 12) versus 125 mmHg (standard deviation 15); p <0.05), augmentation index (78% (standard deviation 8.4) versus 65% (standard deviation 13); p <0.05) and brachial systolic blood pressure (147 mmHg (standard deviation 12) versus 126 mmHg (standard deviation 13); p <0.05) at 26 to 32 weeks' gestation compared with controls. Women who subsequently developed superimposed pre-eclampsia without small for gestational age infants had significantly higher central aortic pressure (142 mmHg (standard deviation 21) versus 125 mmHg (standard deviation 15); p <0.05) at 26 to 32 weeks' gestation compared to controls, and women who delivered a small for gestational age infant had significantly higher adjusted augmentation

index (81% (standard deviation 8.9) versus 68% (standard deviation 12); p <0.05) compared to controls.[253] This study is limited by the small number of participants and the division of participants into multiple outcome groups for comparison. They also assessed vascular function at a relatively late and wide gestational time point, which impacts the clinical utility of these data. The association of vascular function parameters and adverse maternal and perinatal outcome in women with chronic hypertension warrants further exploration.

1.7 Summary

The prevalence of chronic hypertension in pregnancy is increasing. Chronic hypertension is associated with an increased risk of adverse maternal and perinatal outcomes, as well as long term cardiovascular morbidity and mortality risk for the mother. The 2010 NICE 'Hypertension in Pregnancy' guideline states that 'the evidence from trials on treatment of blood pressure does not make it possible to determine the preferred antihypertensive agent for pregnant women with chronic hypertension'.[16] Given the wealth of data from randomised controlled trials comparing antihypertensive treatment outside pregnancy, further investigation of the optimal treatment within pregnancy is warranted.

Previous studies have suggested that Black ethnicity is associated with an increased risk of adverse maternal and perinatal outcome in normotensive women. The impact of maternal characteristics such as ethnicity warrant further investigation in women with chronic hypertension in pregnancy, particularly when choosing the optimal antihypertensive agent. Additionally, exploration of variation in biomarkers and vascular function measures in an ethnically diverse group of women with chronic hypertension in pregnancy may increase our understanding of pathophysiological mechanisms and highlight potential clinical utility of these markers.

CHAPTER 2 HYPOTHESES, RESEARCH QUESTIONS AND PROJECT OBJECTIVES

The subject underpinning the studies conducted within this thesis is chronic hypertension in pregnancy. The hypotheses, research questions and study specific objectives for each stream of work conducted within the PhD programme are outlined below.

2.1 Hypotheses

- The use of antihypertensive agents for the treatment of chronic hypertension in pregnancy improves maternal outcome without adverse effect on perinatal outcome.

- Maternal characteristics such as ethnicity impact the risk of adverse maternal and perinatal outcome in women with chronic hypertension.

- Labetalol and nifedipine demonstrate comparable effectiveness at controlling chronic hypertension in pregnancy, but nifedipine (a calcium-channel blocker) offers greater efficacy in women of Black ethnicity.

- Variation in clinical outcomes in women with chronic hypertension in pregnancy can be explained by longitudinal differences in biomarkers and vascular function measures.

- Ethnic variation in pregnancy outcome in women with chronic hypertension is associated with longitudinal differences in biomarkers and vascular function parameters.

2.2 Research questions and project objectives

2.2.1 Systematic review and meta-analysis assessing the impact of antihypertensive treatment on maternal and perinatal outcomes in pregnancy complicated by chronic hypertension (Chapter 3)

Objectives:

To perform a systematic review and meta-analysis of all randomised controlled trials to date enrolling women with chronic hypertension in pregnancy to answer the following questions:

- Which antihypertensive treatment is associated with fewest episodes of severe hypertension in pregnancy?
- Does frequency of adverse maternal outcomes (e.g. superimposed pre-eclampsia, stroke, death) vary by antihypertensive agent?
- Does frequency of perinatal adverse outcomes (e.g. fetal growth restriction, preterm delivery, neonatal unit admission) vary by antihypertensive agent?

2.2.2 Cohort study investigating the prevalence of adverse perinatal outcomes and associated risk factors in women with chronic hypertension (Chapter 4)

Objectives:

To perform a cohort study of women with chronic hypertension in pregnancy at three UK centres to answer the following research questions:

- What is the risk of adverse maternal and perinatal outcome in women with chronic hypertension in pregnancy in the UK compared with the general pregnant population?
- Which maternal characteristics (e.g. ethnicity, maternal age, level of deprivation, smoking history) are associated with an increased risk of adverse fetal and neonatal outcomes (e.g. stillbirth, fetal growth restriction, preterm delivery)?

2.2.3 Randomised controlled feasibility study comparing labetalol and nifedipine for treatment of chronic hypertension in pregnancy (Chapter 5)

Objectives:

To undertake a randomised controlled feasibility trial in an ethnically diverse group comparing labetalol and nifedipine in pregnant women with chronic hypertension with the following research questions:

- Is enrolment of an ethnically diverse group of pregnant women with chronic hypertension to a randomised controlled trial comparing labetalol and nifedipine as first line antihypertensive treatment feasible?

- Is nifedipine as effective as labetalol at controlling blood pressure in women with chronic hypertension in pregnancy?
- Can potential mechanistic treatment effects be explained by differences in biomarkers (e.g. PlGF, syndecan-1, renin, aldosterone, PCR, ACR) and vascular function parameters (e.g. central aortic pressure, pulse wave velocity, augmentation index)?

2.2.4 Nested cohort studies examining the longitudinal variation in biomarker and vascular function parameters in an ethnically diverse group of pregnant women with chronic hypertension (Chapters 6 and 7)

Objectives:

To assess longitudinal variation in placental, endothelial and renal biomarkers in women with chronic hypertension in pregnancy, and additionally to assess longitudinal variation in vascular function parameters measured using pulse wave analysis in women with chronic hypertension to answer the following questions:

- Do longitudinal changes in biomarker and vascular function parameters pre-date the development of placental pathology (superimposed pre-eclampsia and fetal growth restriction)?
- Does ethnic variation in longitudinal biomarkers and vascular function parameters in women with chronic hypertension in pregnancy exist?

CHAPTER 3 THE IMPACT OF ANTIHYPERTENSIVE TREATMENT ON MATERNAL AND PERINATAL OUTCOMES IN PREGNANCY COMPLICATED BY CHRONIC HYPERTENSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

3.1 Abstract

Chronic hypertension complicates around 3% of all pregnancies. There is evidence that treating severe hypertension reduces maternal morbidity. This study aimed to systematically review randomised controlled trials of antihypertensive agents treating chronic hypertension in pregnancy, to determine the effect of this intervention. Medline (via OVID), Embase (via OVID) and the Cochrane Trials Register were searched from their earliest entries until 30.11.16. All randomised controlled trials evaluating antihypertensive treatments for chronic hypertension in pregnancy were included. Data were extracted and analysed in Stata (version 14.1). Fifteen randomised controlled trials (1166 women) were identified for meta-analysis. A clinically important reduction in the incidence of severe hypertension was seen with antihypertensive treatment versus no antihypertensive treatment/placebo (five studies, 446 women; risk ratio (RR) 0.33, 95% confidence interval (CI) 0.19 to 0.56; I^2 0.0%). There was no difference in the incidence of superimposed pre-eclampsia (seven studies, 727 women; RR 0.74, 95%CI 0.49 to 1.11; I^2 28.1%), stillbirth/neonatal death (four studies, 667 women; RR 0.37, 95%CI 0.11 to 1.26; I^2 0.0%), birthweight (seven studies, 802 women; weighted mean difference -60g, 95%CI -200g to 80g; I^2 0.0%), or small for gestational age (four studies, 369 women; RR 1.01, 95%CI 0.53 to 1.94; I^2 0.0%) with antihypertensive treatment versus no treatment/placebo. Antihypertensive treatment reduces the risk of severe hypertension in pregnant women with chronic hypertension. A considerable paucity of data exists to guide choice of antihypertensive agent. Adequately powered head-to-head randomised controlled trials of commonly used antihypertensive agents are required to inform prescribing.

3.2 Introduction

Chronic hypertension complicates around 3% of all pregnancies.[29,32] There is growing evidence that the incidence is rising with increasing maternal age and obesity.[5,29,39,254] The increased risks of adverse perinatal outcomes for pregnant women with chronic hypertension are well established.[8,45] In addition, controlling severe systolic hypertension has been recommended repeatedly by national and international guidance to reduce the risks of maternal morbidity and mortality.[16,49,57]

There remains some debate regarding the efficacy of treating chronic hypertension in pregnancy before it reaches severe levels due to concerns for fetal growth.[64,129,151,255-257]

Internationally guidelines vary for the management of chronic hypertension in pregnancy.[14] However, the Control of Hypertension in Pregnancy Study (CHIPS), published in 2015, reported that there was no effect of tight blood pressure control (target diastolic 85 mmHg) compared to less tight control (target diastolic 105 mmHg) on a composite outcome of pregnancy loss and high-level neonatal care within the first 48 hours of infant life (31.4% versus 30.7%) and the overall risk of small for gestational age infants (birthweight <10th centile) was not different between groups (16.1% versus 19.7%; odds ratio 0.78, 95% confidence interval 0.56 to 1.08). The frequency of severe hypertension was significantly higher with less-tight control compared to tight control (40.6% versus 27.5%; odds ratio 1.8, 95% confidence interval 1.3 to 2.4).[15] There are likely to be additional benefits of reducing the incidence of severe hypertension through a decrease in short and long-term maternal morbidity and mortality from stroke and other end-organ damage,[49,62,131-133] and potential cost savings with a reduction in healthcare resource use.[134,135]

Given the physiological demands of pregnancy, duration of treatment and potential impacts on maternal and perinatal outcomes, there is a need for evidence on efficacy and safety of antihypertensive treatment specifically in pregnancy complicated by chronic hypertension. Current international guidance points to the lack of evidence for antihypertensive agent prescribing in chronic hypertension in pregnancy.[14,16] As the benefits of tight control blood pressure targets have now been demonstrated in women with hypertension in pregnancy, this study aimed to systematically review and meta-analyse available data from randomised controlled trials specifically in chronic hypertension to establish the efficacy and safety of antihypertensive agents or class of agents.

3.3 Methods

The study protocol for this systematic review was developed in line with the PRISMA-P statement[258] and registered on the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/prospero.asp reference number CRD42015020733).

Literature search

A comprehensive literature review using Medline (via Ovid), Embase (via Ovid) and the Cochrane Trials Register from their earliest entries until the 30th November 2016 was performed. Search strategies were adapted to each database. Searches of exploded MeSH terms ‘pregnancy’, ‘hypertension’ and ‘antihypertensive’ (Embase) or ‘cardiovascular agent’ (Medline) individually were performed, and then combined in each database. For Medline and

Embase searches, a search filter for randomised controlled trials was then applied as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[259] Relevant unpublished data were sought by searching for trials registered on clinicaltrials.gov and ISRCTN (www.isrctn.com), and reviewing thesis titles from the World Cat dissertations and theses database. References of retrieved studies and relevant review articles were also searched using the snowballing approach. No language restrictions were applied.

Study selection criteria

All randomised controlled trials of pregnant women with chronic hypertension comparing an antihypertensive agent with another treatment arm as long-term antepartum management were included. No blood pressure cut-offs were utilised in the eligibility criteria for inclusion, but studies examining acute treatment of severe hypertension via intravenous/fast-acting routes were excluded. Comparisons with other antihypertensive drug(s), placebo, no treatment, or an alternative such as bed rest, were eligible for inclusion. Studies that included participants with gestational hypertension and chronic hypertension were only eligible for inclusion if the data for the women with chronic hypertension population were reported separately to allow fair comparison. Studies that compared management strategies only but did not include a randomised comparison of drug treatments were not eligible for inclusion. Trials that did not report any of the pre-defined outcomes were excluded. Trials that did not include sufficient information on the outcomes (e.g. standard deviations) could not be included in the meta-analysis. No other restrictions were applied to the study search.

Data extraction

The titles, abstracts and selected full texts generated from the literature search were independently screened by authors LMW and FCR. Data from the trials that met all inclusion criteria were manually extracted and entered into a standard extraction table independently from full texts by LMW and FCR. The authors were not masked to the results of the study or authors. Where two articles published results from the same study, individual pertinent outcomes were extracted from both articles without repetition of data extraction. The primary outcomes were maternal severe hypertension (definitions used in each study documented) and neonatal birthweight. In addition, the following secondary outcome measures were recorded for each study; maternal: superimposed pre-eclampsia (definitions used in each study documented), caesarean section delivery, abruption; perinatal: stillbirth/neonatal death, small for gestational age infants (within trial definition), preterm birth (defined as less than 37

completed weeks' gestation), and Apgar score less than seven at five minutes. Details of potential confounders (maternal age, body mass index, ethnicity) were recorded wherever provided in the manuscripts. The PRISMA statement was considered and observed for all procedures and reporting.[260]

Study quality assessment

Each trial was independently quality assessed using the Cochrane Collaboration Risk of Bias tool by LMW and FCR.[259] The risk of bias in each of the following domains was assessed: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias.

Statistical methods

Data were analysed in the statistical package Stata (version 14.1, Stator, College Station, Texas), using the metan suite of commands.[261] All outcomes were analysed on an intention to treat basis. Per-protocol data for an endpoint were excluded from the analysis. Meta-analysis was performed using a fixed effects model where there was more than one study with analysable data. If there was evidence of significant heterogeneity, the meta-analysis was repeated using the random effects model for comparison, however the results presented are from the fixed effects analysis. Initial analysis of treatment effects was performed by class of antihypertensive agent and subsequently by active versus non-active treatment. Treatment effects are presented as estimated differences in mean or risk ratios with 95% confidence intervals. Heterogeneity was quantified via the Tau-squared and I-squared statistics.[262]

3.4 Results

Description of studies

The study selection process is illustrated in the flow chart, Figure 3.1. After removal of duplicates the initial search generated 501 titles and abstracts for review. Following screening, 39 articles underwent full text assessment. 16 articles met inclusion criteria, reporting on 15 trials that recruited a total of 1166 women, with a median of 20 participants per trial (interquartile range 12 to 60 participants per trial).

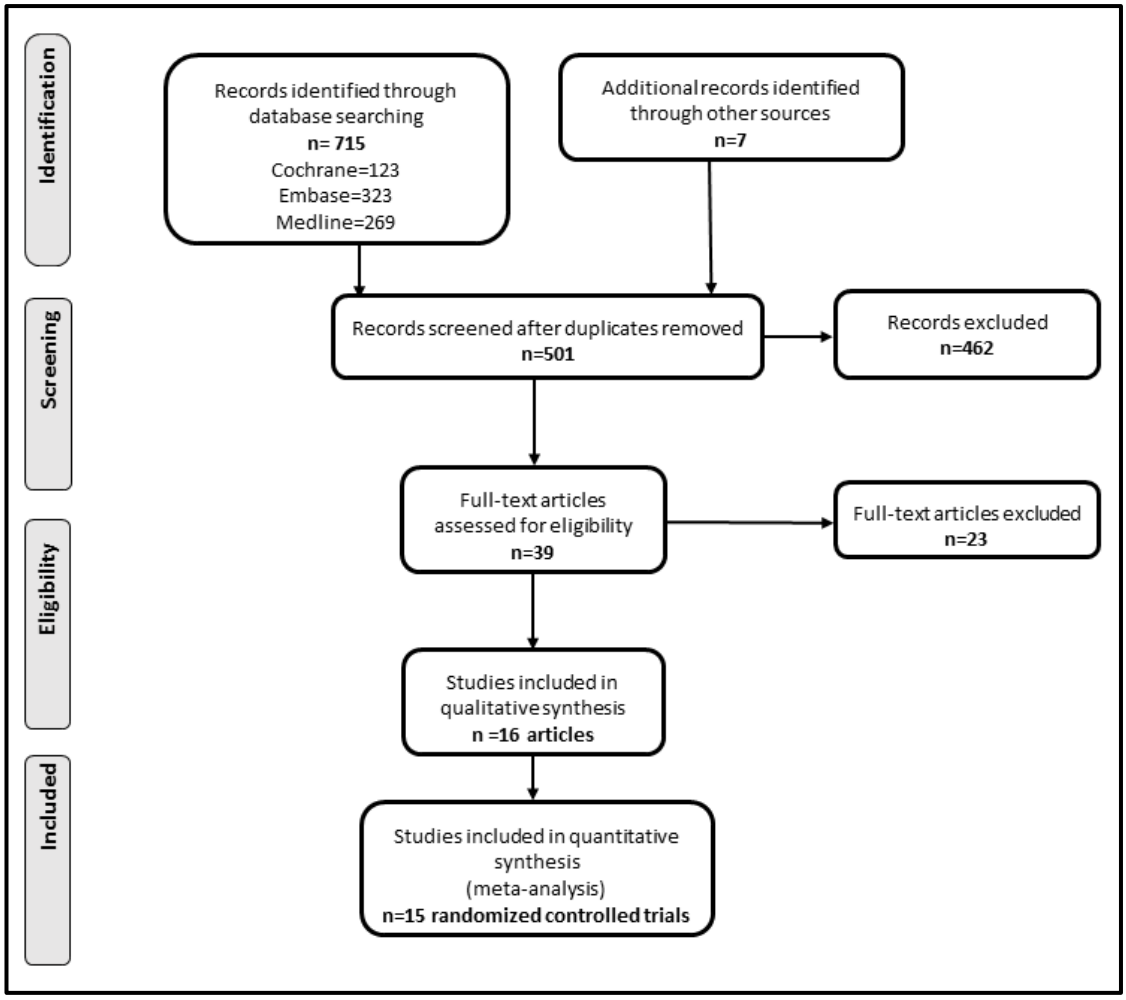


Figure 3.1 Flow chart of articles identified reporting randomised controlled trials of antihypertensive agents for the treatment of chronic hypertension in pregnancy
The characteristics of the studies meeting entry criteria are presented in Table 3.1.

Table 3.1 Characteristics of the studies included in the meta-analysis

Study First Author, Country, Year	Methods	Participants with chronic hypertension	Intervention	Outcomes included in meta-analysis
Arias, USA, 1979[263]	• Participants allocated randomly to antihypertensive treatment or no treatment • No allocation concealment.	• 58 women • History of hypertension before pregnancy (BP >140/90 mmHg) • OR hypertension in 2 consecutive measurements more than 24 hours apart at <20 weeks' gestation • AND diastolic BP <100 mmHg and no end organ damage **Excluded:** • Nulliparous women • Major obstetric or medical problem e.g. diabetes • >20 weeks' gestation	**Active:** A varied combination of: • Methyldopa 750-2000 mg/day • AND/OR hydralazine 75-250 mg/day • AND/OR hydrochlorothiazide 50 mg/day **Versus Non-active:** • No treatment	**Maternal:** • Severe hypertension • Superimposed pre-eclampsia • Mode of delivery **Perinatal:** • Stillbirth/neonatal death • Birthweight • Preterm birth
Butters, UK, 1990[154]	• Double blind randomised controlled trial	• 29 women • Systolic BP 140-170 mmHg or diastolic BP 90-110 mmHg on 2 occasions separated by at least 24 hours between 12 and 24 weeks' gestation in women with known essential hypertension **Excluded:** • Contra-indication to β-blocker	**Active:** • Atenolol 50-200 mg/day **Versus Non-active:** • Placebo tablets	**Perinatal:** • Stillbirth • Birthweight • Small for gestational age
Fiddler, UK, 1983[264]	• Participants mixed population of gestational and chronic hypertension • Stratified randomisation • Open label	• 46 women • Diastolic BP >95 mmHg on 2 occasions at least 24 hours apart <32 weeks' gestation • OR diastolic BP > 105 mmHg on 1 occasion at <32 weeks' gestation **Excluded:** • Diabetes • Multiple pregnancy • Already taking antihypertensive treatment • Significant medical condition	**Active:** • Methyldopa 750-3000 mg/day **Versus Active:** • Oxprenolol 160-640 mg/day	**Maternal:** • Severe hypertension • Mode of delivery **Perinatal:** • Birthweight • Apgar score <7 at 5 minutes
Freire, Brazil, 1988[265]	• Consecutive randomisation allocation • No information on allocation concealment	• 40 women • Known chronic hypertension • Diastolic BP >95 mmHg. **Excluded:** • Proteinuria at study entry • End-organ disease	**Active:** • Methyldopa 250-2000 mg/day **Versus Active** • Pindolol 10-30 mg/day	**Maternal:** • Severe hypertension • Superimposed pre-eclampsia. **Perinatal:** • Stillbirth • Birthweight • Apgar score <7 at 5 minutes
Hirsch, Israel, 1996[266]	• Randomised using serial numbers in blocks of 6 • No information on allocation concealment	• 27 women • Elevated BP prior to pregnancy or diastolic BP 85-99 mmHg at <20 weeks' gestation. **Excluded:** • Known medical or obstetric complication that could affect pregnancy outcome	**Active:** • Pindolol 10-20 mg/day **Versus Non-active:** • Placebo tablets	**Maternal:** • Severe hypertension **Perinatal:** • Birthweight • Small for gestational age

		• β-blockers contraindicated		• Apgar score <7 at 5 minutes
Horvath, Australia, 1985[267]	• Participants mixed population of gestational and chronic hypertension • Double-blind, randomised trial • Participants entered in numerical sequence	• 16 women • Known essential hypertension • OR failure of hypertension to resolve 12 weeks postpartum from previous pregnancy • OR BP >130/85 mmHg on 2 or more occasions	**Active:** • Methyldopa 250-2000 mg/day **Versus Non-active:** • Clonidine 150-1200 µg/day	**Perinatal:** • Stillbirth/neonatal death
Kahhale, Brazil, 1985[268]	• Women divided into two groups – treatment and control • No information regarding concealment	• 100 women • BP >140/90 mmHg before 20 weeks' gestation **Excluded:** • Proteinuria at study entry • Contraindication to β-blockers	**Active:** • Pindolol 10-30 mg/day **Versus Non-active:** • No treatment	**Perinatal:** • Stillbirth • Birthweight • Apgar score <7 at 5 minutes
†Mutch, UK, 1977[269]	• Participants mixed population of gestational and chronic hypertension • Randomly allocated • Open label	• 202 women • BP >140/90 mmHg on 2 occasions at least 24 hours apart before 28 weeks' gestation **Excluded:** • BP at study entry >170 mmHg systolic or >110 mmHg diastolic • Multiple pregnancy • Rhesus incompatibility • Severe maternal disease	**Active:** • Methyldopa – dosing regimen not specified **Versus Non-active:** • No treatment	**Maternal:** • Severe hypertension • Superimposed pre-eclampsia • Mode of delivery
Parazzini, Italy, 1998[177]	• Participants mixed population of gestational and chronic hypertension • Computer generated randomisation list • Open label	• 126 women • Known chronic hypertension prior to pregnancy with 2 consecutive diastolic BP >90 mmHg • OR diastolic BP >90 mmHg before 20 weeks' gestation **Excluded:** • Chronic disease e.g. diabetes, renal disease • Fetal malformations • Already on antihypertensive treatment • Contraindications to nifedipine	**Active:** • Nifedipine slow release 20-80 mg/day **Versus Non-active:** • No treatment	**Perinatal:** • Birthweight
†Redman, UK, 1976[183]	• Participants mixed population of gestational and chronic hypertension • Allocated randomly to treatment group • Open label	• 208 women • BP >140/90 mmHg on 2 occasions at least 24 hours apart before 28 weeks' gestation. **Excluded:** • Severe hypertension at study entry (systolic BP >170 mmHg or diastolic BP >110 mmHg) • Already on antihypertensive treatment • Multiple pregnancy • Diabetes • Rhesus immunisation	**Active:** • Methyldopa – dosing regimen not specified **Versus Non-active:** • No treatment	**Perinatal:** • Stillbirth/neonatal death • Birthweight
Sibai, USA, 1984[270]	• Participants taking diuretics randomised to	• 20 women	**Active:**	**Maternal:** • Superimposed pre-eclampsia

	continue or discontinue treatment • Open label	• Long-term history of hypertension, diastolic BP >90 mmHg and <110 mmHg • Receiving diuretics prior to pregnancy	• Diuretics – specific agent(s) and doses not specified **Versus Non-active:** • No treatment (diuretics discontinued)	• Mode of delivery **Perinatal:** • Birthweight • Preterm birth • Apgar score <7 at 5 minutes
Sibai, USA, 1990[271]	• Computer generated randomization via list of numbers • Open label	• 263 women • History of chronic hypertension prior to pregnancy **Excluded:** • Medical complications other than chronic hypertension	**Active:** • Methyldopa 750-4000 mg/day **Versus Active:** • Labetalol 300-2400 mg/day **Versus Non-active:** • No treatment	**Maternal:** • Superimposed pre-eclampsia • Mode of delivery • Abruption **Perinatal:** • Stillbirth/neonatal death • Birthweight • Preterm birth
Steyn, South Africa, 1997[272]	• Double blind randomised placebo controlled trial • Computer generated randomisation numbers, using balanced block method	• 138 women • Diastolic BP persistently >80 mmHg between 12 and 20 weeks' gestation without proteinuria **Excluded:** • Multiple pregnancy • Bradycardia on ECG	**Active:** • Ketanserin 40-80 mg/day **Versus Non-active:** • Placebo tablets	**Maternal:** • Severe hypertension • Superimposed pre-eclampsia • Abruption **Perinatal:** • Stillbirth/neonatal death
Voto, Argentina, 1990[273]	• Participants mixed population of gestational and chronic hypertension • Randomised comparative study • Open label	• 49 women • Known chronic hypertension with BP >159/99 mmHg twice 24 hours apart **Excluded:** • Women requiring more than 1 drug to control BP	**Active:** • Atenolol 50-200 mg/day **Versus Active:** • Methyldopa 500-2000 mg/day **Versus Active:** • Ketanserin 80-120 mg/day	**Maternal:** • Superimposed pre-eclampsia
Weitz, USA, 1987[274]	• Double blind randomised study	• 25 women • Chronic hypertension, BP 140/90 mmHg on 2 occasions >6 hours apart • No proteinuria • Singleton pregnancies • <34 weeks' gestation	**Active:** • Methyldopa 750-2000 g/day **Versus Non-active:** • Placebo tablets	**Maternal:** • Superimposed pre-eclampsia **Perinatal:** • Stillbirth/neonatal death
Welt, USA, 1981[275]	• Prospective cohort study with sub-group randomised to treatment • Not clear if either clinician and/or participant blinded to treatment allocation	• 21 women • With documented pre-pregnancy history of elevated BP >140/90 mmHg on 2 occasions >6 hours apart • OR in first 2 trimesters of pregnancy • OR undocumented history of hypertension for which the patient was taking antihypertensive treatment before or during pregnancy **Excluded:** • Diabetes requiring insulin • Multiple pregnancy	**Active:** • Methyldopa 750 mg/day- maximum dose not given **Versus Active:** • Hydralazine 75 mg/day- maximum dose not given **Versus Non-active:** • Placebo tablets	**Maternal:** • Severe hypertension • Superimposed pre-eclampsia **Perinatal:** • Small for gestational age

*BP = blood pressure *Participants randomised to antihypertensive treatment (not to an agent) versus no antihypertensive treatment. †Papers reporting on the same study population.*

All studies included in the meta-analysis were completed prior to 1998. Ten of the trials were conducted in a pre-defined chronic hypertension cohort alone,[154,263,265,266,268,270-272,274,275] and the remaining five reported outcomes for a subgroup of women with chronic hypertension.[177,183,264,267,269,273] Six studies were head-to-head comparisons of two or more antihypertensive agents (435 women),[264,265,267,271,273,275] four were placebo-controlled studies of a single antihypertensive agent (219 women),[154,266,272,274] and five were studies of single antihypertensive agent compared to no treatment (714 women).[177,183,263,268-270]

Table 3.2 Studies excluded from the meta-analysis and rational

Study (Author, Country, Year published)	Reason for exclusion and study details
Antony, South Africa, 1990[276]	Study participants had gestational and not chronic hypertension. **Methods:** Prospective, randomised block design, no further details given. **Participants:** 60 women at 28-36 weeks' gestation with mean 24-hour diastolic BP 100-120 mmHg +/- proteinuria. **Intervention:** Indoramin 50 mg twice daily versus methyldopa 1 g twice daily versus placebo 1 tablet daily.
Bolte, Netherlands, 1998[277]	Study participants had gestational or chronic hypertension. Outcomes for those with chronic hypertension not reported separately. **Methods:** Randomised, open-label multicentre trial. **Participants:** 31 women, 26 to 32 weeks' gestation with diastolic BP >110 mmHg and previously normotensive or in women with chronic hypertension diastolic BP >20 mmHg compared to BP at <20 weeks'. **Intervention**: IV ketanserin 5 mg bolus then 4 mg/hour versus IV dihydralazine 1 mg/hour.
Bott-Kanner, Israel, 1992[278]	Study participants had gestational or chronic hypertension. Outcomes for those with chronic hypertension not reported separately. **Methods:** Randomised, double-blind trial. Women randomised in blocks of 6 using serial numbers. **Participants:** 60 women before 35 weeks' gestation with diastolic BP 85-99 mmHg. **Intervention:** Pindolol 5 mg twice daily or placebo 1 tablet twice daily.
Cruickshank, UK, 1991[279]	Study participants had gestational and not chronic hypertension. **Methods:** Randomised open-label trial, using numbered sealed envelopes. **Participants:** 114 women with singleton pregnancies between 24 and 39 weeks' gestation, diastolic BP >90 mmHg for >24 hours in absence of proteinuria. **Intervention:** Labetalol 100 mg twice daily versus no treatment.
Faneite, Venezuela, 1988[280]	Study participants had gestational or chronic hypertension. Outcomes for those with chronic hypertension not reported separately. **Methods:** Randomised trial. **Participants:** 31 women >14 weeks' gestation, with BP >140/90 mmHg and <170/110 mmHg on 2 occasions. **Intervention:** Mepindolol 5 mg once daily versu0s methyldopa 250 mg twice daily.
Gallery, Australia, 1979[281]	Study participants had gestational or chronic hypertension. Outcomes for those with chronic hypertension not reported separately. **Methods:** Randomised comparison study. **Participants:** 56 women at any gestation with sitting diastolic BP >95 mmHg on 2 occasions at least 24 hours apart or 100 mmHg on two occasions at least 8 hours apart. **Intervention:** Oxprenolol versus methyldopa. Doses not specified.
Gallery, Australia, 1985[282]	Study participants had gestational or chronic hypertension. Outcomes for those with chronic hypertension not reported separately. **Methods:** Randomised open study, allocation by random number series. **Participants:** 183 women with singleton pregnancies and sitting diastolic BP of >90 mmHg on two occasions at least 24 hours apart or >95 mmHg on 2 occasions 12 hours apart or >100 mmHg on 2 occasions 8 hours apart.

	Intervention: Oxprenolol 40 mg twice daily versus methyldopa 250 mg twice daily.
Hall, South Africa, 2000[283]	Study participants had pre-eclampsia, gestational or chronic hypertension. Outcomes for those with chronic hypertension not reported separately. **Methods:** Randomised single blind controlled trial. Computer generated balanced blocks of 50 numbers. Women allocated using consecutive, numbered, opaque envelopes containing medication. **Participants:** 150 women with severe early onset pre-eclampsia or hypertension and BP not controlled with methyldopa 2 mg/daily. **Intervention:** Nifedipine 10 mg three times daily versus prazosin 1 mg three times daily.
Henderson-Smart, Australia, 1984[284]	Details of participants with chronic hypertension not stated. **Methods:** Reporting neonatal outcomes of infants born to women with hypertension in pregnancy who were entered in a prospective randomised double blind trial. **Participants:** 95 infants born to mothers treated with clonidine hydrochloride and methyldopa. **Intervention:** Clonidine hydrochloride 150-1200 µg/day versus methyldopa 250-2000 mg/day.
Hogstedt, Sweden, 1985[285]	Study participants had gestational or chronic hypertension. Outcomes for those with chronic hypertension not reported separately. **Methods:** Randomised open controlled trial. **Participants:** 161 women in antenatal care with diastolic BP > 90 mmHg on two occasions at least 6 hours apart, confirmed the following day with diastolic BP >90 mmHg for at least 2 out of 4 BP readings. **Intervention:** 50 mg metoprolol and 25 mg hydralazine twice daily versus no treatment.
Jannet, France, 1994[286]	Study participants had gestational or chronic hypertension or pre-eclampsia. Outcomes for those with chronic hypertension not reported separately. **Methods:** Randomised comparative trial. Computer generated random numbers, allocated using sealed envelopes. **Participants:** 100 women with singleton pregnancies at >20 weeks' gestation with systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg on 2 successive measurements. **Intervention:** Nicardipine 20 mg three times daily versus slow release metoprolol 200 mg once daily.
Lardoux, France, 1988[287]	Study participants had gestational or chronic hypertension. Outcomes for those with chronic hypertension not reported separately. **Methods:** Randomised open comparative trial. **Participants:** 63 women between 7 and 36 weeks' gestation with diastolic BP > 90 mmHg on two occasions at least 8 days apart. **Intervention:** Methyldopa 500 mg a day versus labetalol 400 mg a day versus acebutolol 400 mg a day.
Leather, UK, 1968[288]	Outcome data not presented with adequate statistical information to allow inclusion in the meta-analysis. **Methods:** Randomised controlled trial. **Participants:** 100 women with diastolic BP > 90 mmHg on two occasions at least 48 hours apart. **Intervention:** Bendroflumethiazide 5-10 mg daily and methyldopa 400-2000 mg daily versus no treatment.
Livingstone, Australia, 1983[289]	Study participants had gestational and not chronic hypertension. **Methods:** Randomised prospective study, no further details given. **Participants:** 28 women with BP > 140/90 mmHg on 2 consecutive readings at least 24 hours apart. **Intervention:** Propanolol versus methyldopa. Doses not specified.
Moore, UK, 1982[290]	Study participants had gestational or chronic hypertension. Outcomes for women with chronic hypertension not reported separately. **Methods:** Randomised trial, no further details given. **Participants:** 74 women at < 36 weeks' gestation with systolic BP > 170 mmHg and/or diastolic BP > 110 mmHg. **Intervention:** Labetalol 100 mg four times daily versus 250 mg methyldopa four times daily.
Plouin, France, 1988[291]	Study participants had gestational or chronic hypertension. Outcomes for women with chronic hypertension not reported separately. **Methods:** Randomised open controlled trial. Stratified randomisation using blinded envelopes. **Participants:** 176 women with a singleton pregnancy, gestational age between 12 and 34 weeks and diastolic BP >89 mmHg on 2 separate occasions. **Intervention:** Labetalol 400 mg in two doses versus methyldopa 500 mg in two doses.
Rosenfeld, Israel, 1986[292]	Study participants had gestational or chronic hypertension. Outcomes for those with chronic hypertension not reported separately. **Methods:** Randomised study, no further details given.

	Participants: 44 women at <36 weeks' gestation with systolic BP >150 mmHg or diastolic BP >90 mmHg on 2 separate occasions at least 24 hours apart. **Intervention:** Hydralazine 25 mg twice daily versus hydralazine 25 mg twice daily and pindolol 5 mg twice daily.
Steyn, South Africa, 2001[293]	Reporting data from same trial as Steyn 1997[272], reported no additional outcomes. **Methods:** Randomised double blind controlled trial. Computer generated balanced block structure. **Participants:** 102 women between 12 and 20 weeks' gestation with diastolic BP >80 mmHg without proteinuria. **Intervention:** Ketanserin 20 mg twice daily and aspirin 75 mg once daily versus placebo 1 tablet twice daily and aspirin 75 mg once daily.
Tuimala, Finland, 1988[294]	Study participants had gestational and not chronic hypertension. **Methods:** Randomised trial, no further details given. **Participants:** 51 women with BP >149/94 mmHg x 2 in sitting position after 2 days bed rest in hospital. **Intervention:** Atenolol 50-100 mg/day versus pindolol 10-20 mg/day. If needed, hydralazine 150 mg/day added.
Vigil-De Gracia, Panama, 2014[295]	Three arm pilot study including a third active treatment arm of aspirin. **Methods:** Randomised open label pilot trial. Computer generated code with block size of six, allocation through sealed envelopes. **Participants:** 63 women at <20 weeks' gestation with systolic BP 90-109 mmHg **Intervention:** Furosemide 20 mg once daily versus amlodipine 5mg once daily versus aspirin 75 mg once daily.
Voto, Argentina, 1987[296]	Study participants had gestational or chronic hypertension or pre-eclampsia. Outcomes for those with chronic hypertension not reported separately. **Methods:** Randomised open study, no further details given. **Participants:** 20 women with systolic BP >159 mmHg and/or diastolic BP >99 mmHg recorded twice 24 hours apart. **Intervention:** Ketanserin 20-80 mg daily versus methyldopa 500-2000 mg daily.
Wichman, Sweden, 1984[297]	Study participants had gestational and not chronic hypertension. **Methods:** Randomised placebo controlled trial. Selective allocation. **Participants:** 52 women at <37 weeks' gestation with systolic BP >140 mmHg or diastolic BP >90 mmHg or if there was an elevation of >30 mmHg systolic or >15 mmHg diastolic from previous readings. **Intervention:** Metoprolol 50 mg twice daily versus placebo 1 tablet twice daily.
Wide-Swensson, Sweden, 1995[298]	Study participants had gestational and not chronic hypertension. **Methods:** Randomised parallel double blind multicentre trial. Block randomisation by numbers, allocation by sealed envelope. **Participants:** 118 women with singleton pregnancy, gestational age between 25 and 37 weeks' and diastolic BP between >95 mmHg and <110 mmHg. **Intervention:** Isradipine slow release 5 mg twice daily versus placebo 1 tablet twice daily.

IV= intravenous, BP=blood pressure

Of the 23 articles that were excluded, 14 studies included a mixed population of gestational and chronic hypertension and did not report outcomes separately, six studies included only gestational hypertension, one paper reported no additional outcomes for a trial already included in the meta-analysis (Table 3.2). In addition, Leather and colleagues reported a randomised controlled trial in 1968 that recruited 47 chronic hypertensive participants randomised to bendroflumethiazide and methyldopa versus no treatment. This paper could not be included due to inadequate reporting of the statistical information relating to the outcomes, prohibiting inclusion of the data in the meta-analysis.[288] Leather and colleagues concluded that the treatment of 'early hypertension' (present before 20 weeks gestation) resulted in a longer pregnancy, increased birthweight and reduced perinatal mortality. A pilot

study by Vigil-De Gracia and colleagues in 2014, compared furosemide, amlodipine and aspirin in a three arm randomised controlled trial, and found no significant difference in outcomes between all treatment arms.[295] These data could not be included in the active versus non-active treatment meta-analysis, as the third arm of aspirin was considered active treatment given that the other arms did not receive this agent. In addition, the data from the amlodipine and furosemide arms could not be included in the antihypertensive treatment versus antihypertensive treatment meta-analysis as there are no other head-to-head trials evaluating calcium-channel blockers or diuretics for comparison.

Table 3.3 Definitions of severe hypertension and superimposed pre-eclampsia for each included study

Study (Author, Country, Year)	Definition of severe hypertension	Definition of superimposed pre-eclampsia
Arias, USA, 1979[263]	'Pregnancy aggravated hypertension': >28 weeks' gestation diastolic BP >100 mmHg in 2 consecutive readings 6 or more hours apart	>1+ proteinuria or more than 300 mg/L protein in 24-hour collection with 'pregnancy aggravated hypertension' (see definition of severe hypertension)
Butters, UK, 1990[154]	Not reported	Not reported
Fiddler, UK, 1983[264]	Admitted to hospital for hypertension: diastolic BP >110 mmHg	Not reported
Freire, Brazil, 1988[265]	Diastolic BP persistently >110 mmHg	Systolic BP increased by 30 mmHg or diastolic BP increased by 20 mmHg for 2 consecutive readings at least 6 hours apart OR proteinuria OR oedema
Hirsch, Israel, 1996[266]	Uncontrolled elevation of diastolic BP >100 mmHg	Not reported
Horvath, Australia, 1985[267]	Not reported	Not reported
Kahhale, Brazil, 1985[268]	Not reported	BP >170/110 mmHg or proteinuria <37 weeks' gestation
*Mutch, UK, 1977[269]	Systolic BP >170 mmHg or diastolic BP >110 mmHg on 2 occasions >4 hours apart	Oedema, proteinuria from mid-stream urine in absence of infection and raised plasma urate
Parazzini, Italy,1998[177]	Not reported	Not reported
*Redman, UK, 1976[183]	Systolic BP >170 mmHg or diastolic BP >110 mmHg on 2 occasions >4 hours apart	Oedema, proteinuria from mid-stream urine in absence of infection and raised plasma urate
Sibai, USA, 1984[270]	Not reported	Not defined but reported as confirmed superimposed pre-eclampsia
Sibai, USA, 1990[271]	Systolic BP >160 mmHg or diastolic BP >100 mmHg	Proteinuria (>1 g/24hrs) or elevated uric acid (>=6 mg/dL) during second half of pregnancy
Steyn, South Africa, 1997[272]	Single diastolic BP >120 mmHg OR 2 consecutive readings of 110 mmHg at least 4 hours apart	Single diastolic BP >110 mmHg or 2 consecutive measurements of 90 mmHg or more at least 4 hours apart with proteinuria 300 mg/L on 24-hour collection OR 2+ proteinuria on dipstick
Voto, Argentina, 1990[273]	Not reported	Additional proteinuria
Weitz, USA, 1987[274]	Not reported	Sudden rise in systolic BP >30 mmHg or diastolic BP >15 mmHg and sudden weight gain >2 lbs per week OR proteinuria 2+ or more on dipstick
Welt, USA, 1981[275]	Diastolic BP >100 torr on 2 occasions 6 or more hours apart	Proteinuria >trace on dipstick or >300 mg/L in 24 hours, oedema, or both

*BP=blood pressure. *Papers reporting the same study population.*

Definitions of severe hypertension and superimposed pre-eclampsia for each included study are listed in Table 3.3. Minimum diastolic and systolic blood pressure eligibility cut-offs ranged from 80 to 99 mmHg and 140 to 160 mmHg respectively. Two studies excluded women with proteinuria,[265,274] three studies included women with proteinuria at study entry,[264,267,273] and the remainder of studies did not specify presence or absence of proteinuria in their methods. Six studies excluded multi-fetal pregnancies[263,264,270,271,274,275]; the remainder either included women with multi-fetal pregnancies or did not specify inclusion or exclusion in their methods. Maternal age was the only potential confounding baseline characteristic consistently reported. This ranged from 28 to 33 years and no adjustment was deemed pertinent to this analysis. Body mass index was not reported in any of the trials, but six studies reported maternal weight at trial entry. Ethnicity of the participants was not considered or recorded in any of the trials.

Risk of bias in included studies

All studies were assessed to be at high risk of bias apart from Steyn et al,[272] which was assigned unclear risk of bias. Full details of the allocated risk of bias scoring displayed in Figure 3.2. No formal assessment of socioeconomic settings of the studies was made given the small number of studies, but all were from middle or high income countries (see Table 3.1).

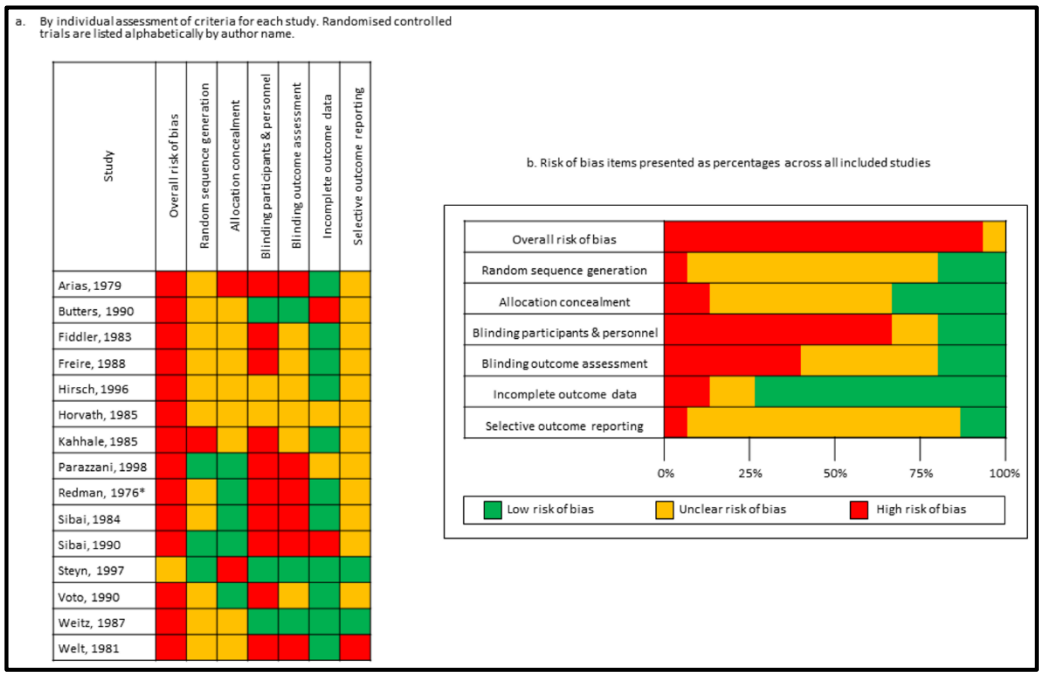


Figure 3.2 Risk of bias assessment of each study included in the meta-analysis

A. *By individual assessment of criteria for each study. Randomised controlled trials are listed alphabetically by author name.*

B. *Risk of bias items presented as percentages across all included studies*

**Redman[183] (1976) and Mutch[269] (1977) both publish data from the same study, only the Redman paper has been assessed for risk of bias. Risk of bias summary showing review authors' judgments about each risk of bias domain in randomised controlled trials on efficacy of antihypertensive treatment for chronic hypertension in pregnancy.*

Effects of intervention (active versus non-active treatment)

Antihypertensive treatment reduces the incidence of severe hypertension in pregnancy complicated by chronic hypertension compared with no antihypertensive or placebo, with a risk ratio of 0.33 (95% confidence interval 0.19 to 0.56), based on 446 women from five studies. The risk of superimposed pre-eclampsia was not significantly different between those randomised to active versus non-active treatment; risk ratio 0.74 (95% confidence interval 0.49 to 1.11: 727 women, seven studies) (Figure 3.3).

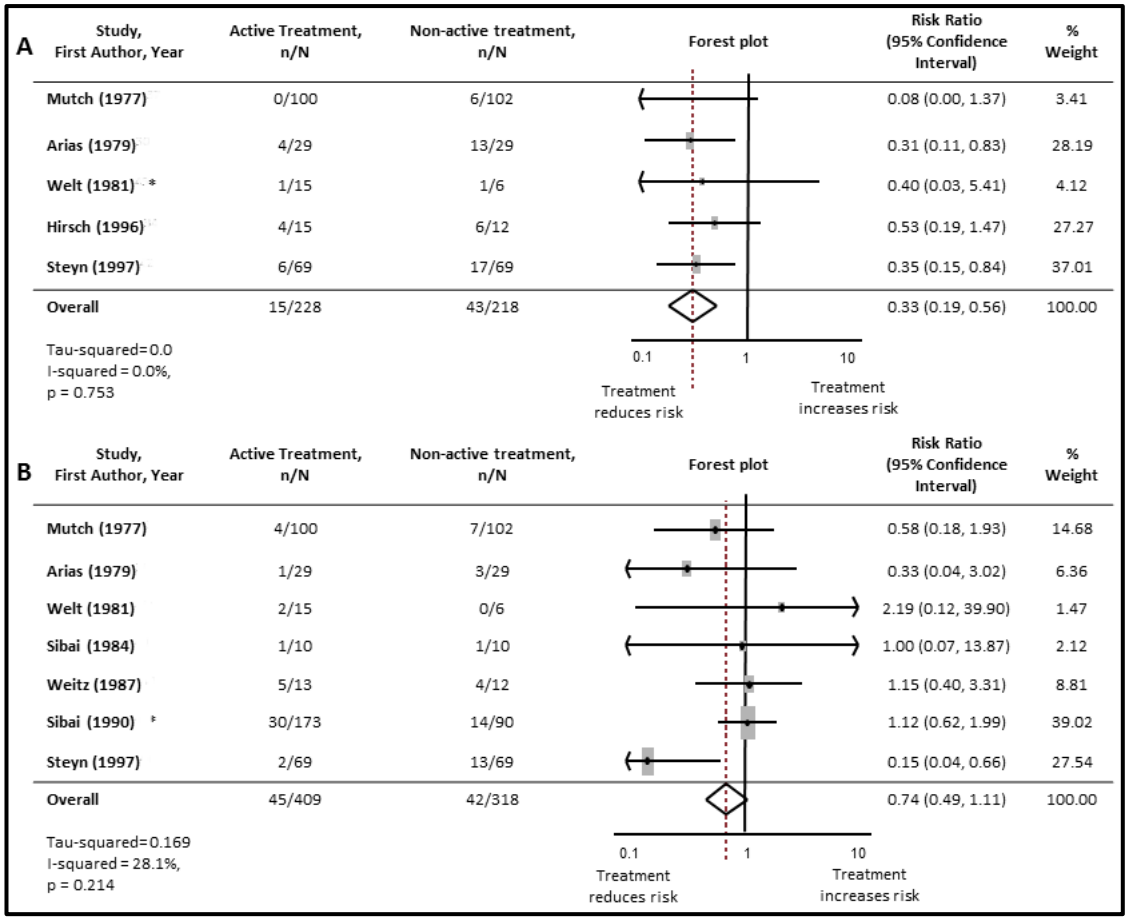


Figure 3.3 Maternal outcomes: active versus non-active treatment

A. *Severe hypertension*
B. *Superimposed pre-eclampsia*

**Where studies had more than one active treatment arm, the data from the active treatment arms were pooled and compared with the non-active treatment data. Studies are listed in order of the year they were published. Antihypertensive agents used in each study are listed in Table 3.1. The number of participants experiencing severe hypertension or superimposed pre-eclampsia in each treatment group are denoted as 'n', with the total number of participants with chronic hypertension in each study arm denoted as 'N'.*

Perinatal outcomes were assessed to determine the potential fetal and neonatal risks associated with antihypertensive use when compared to non-active treatment. The analysis of stillbirth and neonatal death demonstrated a non-significant reduction with the use of antihypertensive treatment: risk ratio 0.37 (95% confidence interval 0.11 to 1.26: 667 women, four studies). Birthweight was not significantly different when active versus non-active treatments were compared (-60g weighted mean difference, 95% confidence interval -200g to 80g; 802 women, seven studies). There was no difference in small for gestational age infants with the use of antihypertensive agents (risk ratio 1.01, 95% confidence interval 0.53 to 1.94; 369 women, four studies) (Figure 3.4).

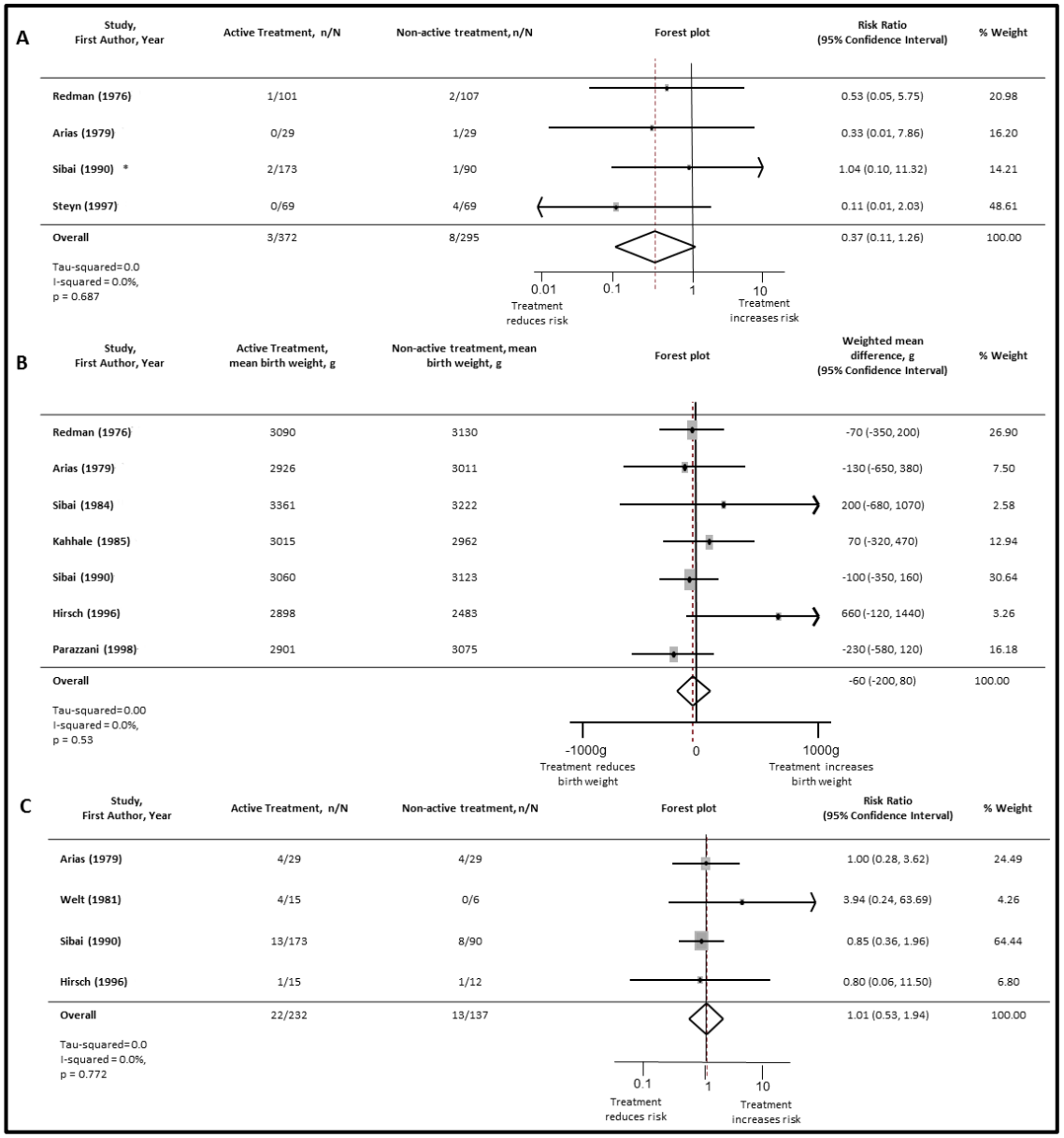


Figure 3.4 Perinatal outcomes: active versus non-active treatment

A. *Stillbirth or neonatal death*
B. *Birthweight*
C. *Small for gestational age infants*

**Where studies had more than one active treatment arm, the data from the active treatment arms were pooled and compared with the non-active treatment data. Studies are listed in order of the year they were published. Antihypertensive agents used in each study are listed in Table 3.1. The number of participants experiencing a stillbirth/neonatal death or small for gestational age infant in each treatment group are denoted as 'n', with the total number of participants with chronic hypertension in each study arm denoted as 'N'.*

A single study by Butters and colleagues (1991) comparing atenolol to placebo found a significant reduction in birthweight and increase in small for gestational age in the active treatment arm.[154] Given the degree of heterogeneity, these results were explored further with

Egger's test. This demonstrated the Butters study[154] as an outlier (Figure 3.5).When this study was included in the meta-analysis, weighted mean difference in birthweight did not reach significance, -100g (95% confidence interval -240g to 40g; I^2 49.6%) and similarly though the risk of small for gestational age increased, it did not reach significance (risk ratio 1.58, 95% confidence interval 0.88 to 2.85; I^2 38.6%).

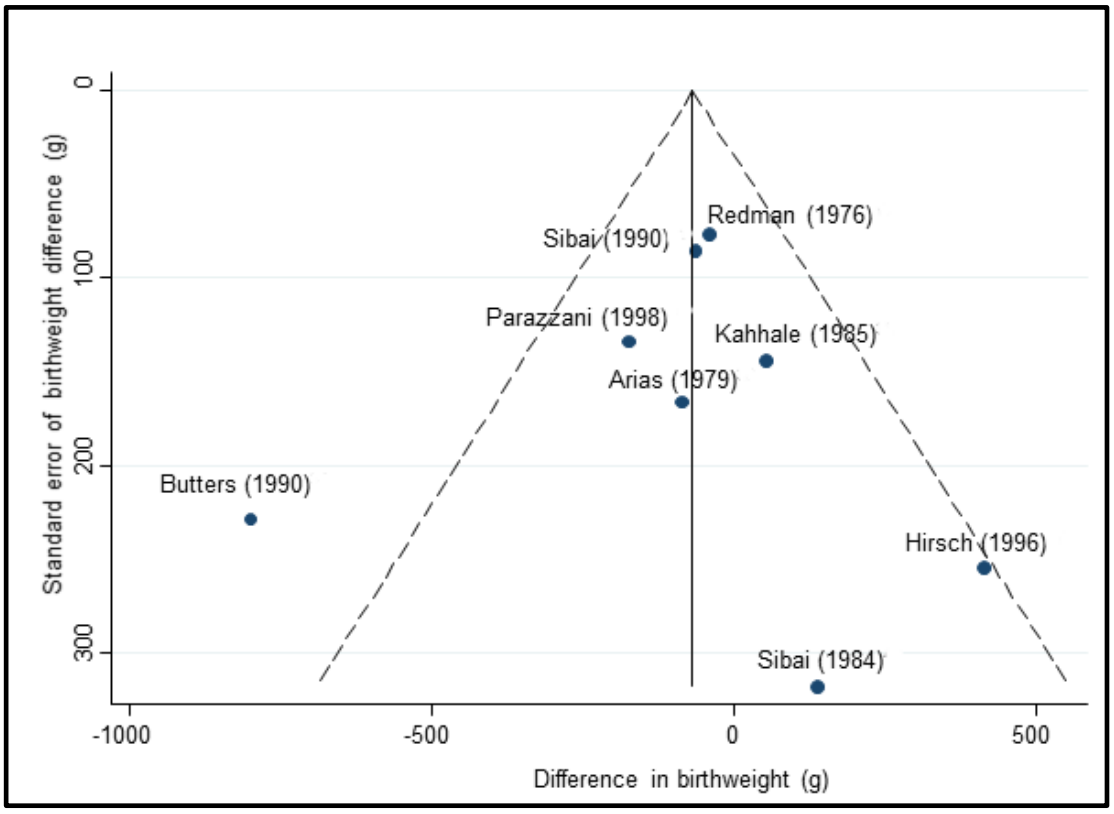


Figure 3.5 Funnel plot comparing birthweight difference between studies
Funnel plot demonstrating Butters and colleagues[154] (1990) (atenolol versus placebo) is an outlier within the meta-analysis of birthweight when comparing active and non-active treatment. Antihypertensive agents used in each study are listed in Table 3.1.

The additional maternal and perinatal outcomes meta-analysed between active and non-active arms are listed in Table 3.4. There were no additional significant differences.

Table 3.4 Summary of meta-analysis findings comparing active with non-active treatment and the effect on maternal and perinatal outcomes in pregnancy complicated by chronic hypertension

Outcome	Number of studies reporting outcome	Total participants	Risk ratio/ weighted mean difference	Confidence Interval, 95%	Degree of heterogeneity, I^2
Maternal					
Severe hypertension	5	446	0.33	0.19 to 0.56	0.0%
Superimposed pre-eclampsia	7	727	0.74	0.49 to 1.11	28.1%
Caesarean section delivery	4	543	1.23	0.92 to 1.63	0.0%
Abruption	2	401	0.35	0.10 to 1.27	20.9%
Perinatal					
Stillbirth/Neonatal death	4	667	0.37	0.11 to 1.26	0.0%
Birthweight (g)	7	802	-60	-200 to 80g	0.0%
Small for gestational age	4	369	1.01	0.53 to 1.94	0.0%
Gestation at delivery (weeks)	7	785	0.10	-0.05 to 0.24	83.7%
Preterm birth	3	341	1.23	0.58 to 2.54	0.0%
Apgar score <7 at 5 minutes	4	410	1.13	0.40 to 3.20	0.0%

Risk ratios provided where binary data was analysed and weighted mean difference given for continuous outcomes.

Table 3.5 Summary of meta-analysis findings comparing methyldopa with other antihypertensive agents and the effect on maternal and perinatal outcomes in pregnancy complicated by chronic hypertension

Outcome	Number of studies reporting outcome	Total participants	Risk ratio/ weighted mean difference	Confidence Interval, 95%	Degree of heterogeneity, I^2
Maternal					
Severe Hypertension	3	101	1.13	0.71 to 1.81	36.4%
Superimposed pre-eclampsia	4	277	0.99	0.62 to 1.58	0.0%
Perinatal					
Stillbirth/Neonatal death	2	186	2.24	0.35 to 14.28	0.0%
Birthweight (g)	3	259	50	-200 to 290	0.0%

Risk ratios provided where binary data was analysed and weighted mean difference given for continuous outcomes.

Effects of intervention (antihypertensive agent versus antihypertensive agent)

Due to the small number of studies, comparison of antihypertensive agents was restricted to methyldopa versus other classes of antihypertensive, and where possible methyldopa versus beta-blockers (Table 3.5). There was no difference in incidence of severe hypertension between agents when methyldopa was compared with other antihypertensive treatments. Two head-to-head studies (86 women) reported incidence of severe hypertension comparing methyldopa and beta-blocker antihypertensive treatment: risk ratio 0.85 (95% confidence interval 0.57 to 1.37). There was no difference in the incidence of superimposed pre-eclampsia when methyldopa was compared with other antihypertensive agents. There were additionally no significant differences in perinatal outcomes between antihypertensive agents. Forest plots of these meta-analyses are presented in Figures 3.6 and 3.7.

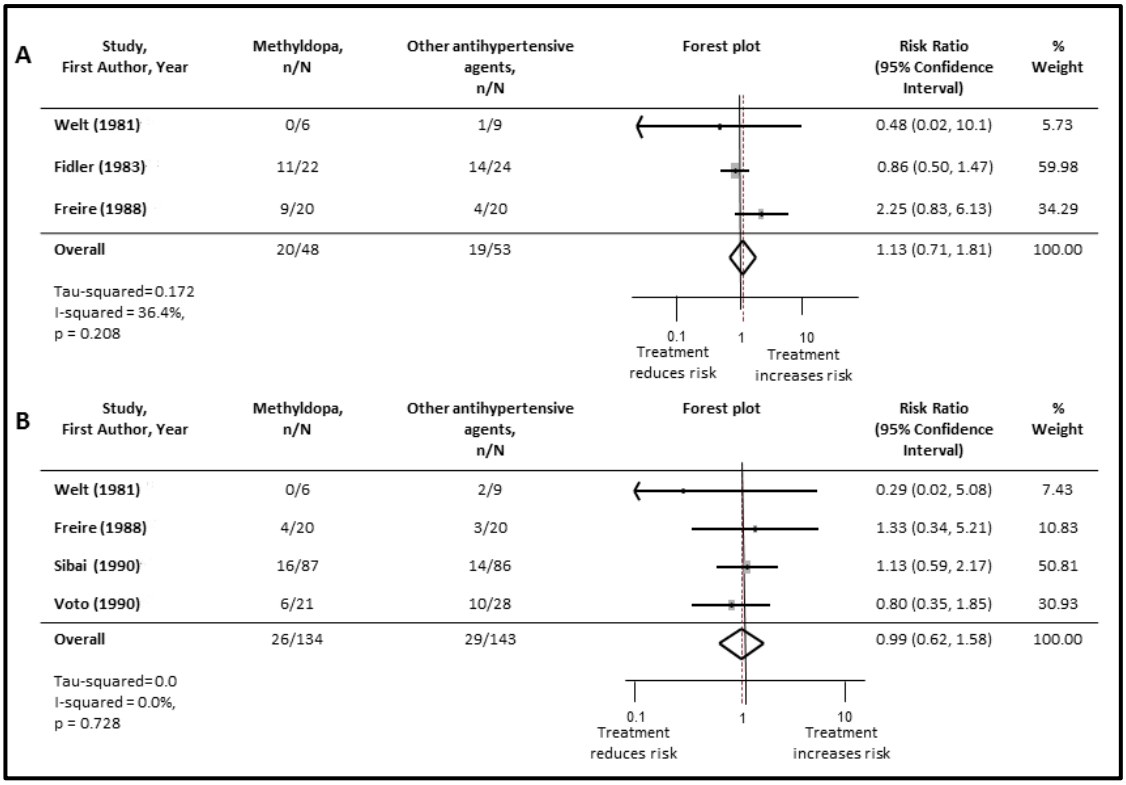


Figure 3.6 Maternal outcomes: comparison of methyldopa versus other antihypertensive agents

A. *Severe hypertension*
B. *Superimposed pre-eclampsia*

Studies listed in order of the year they were published. Antihypertensive agents used in each study are listed in Table 3.1. The number of participants experiencing severe hypertension or superimposed pre-eclampsia in each treatment group are denoted as 'n', with the total number of participants with chronic hypertension in each study arm denoted as 'N'.

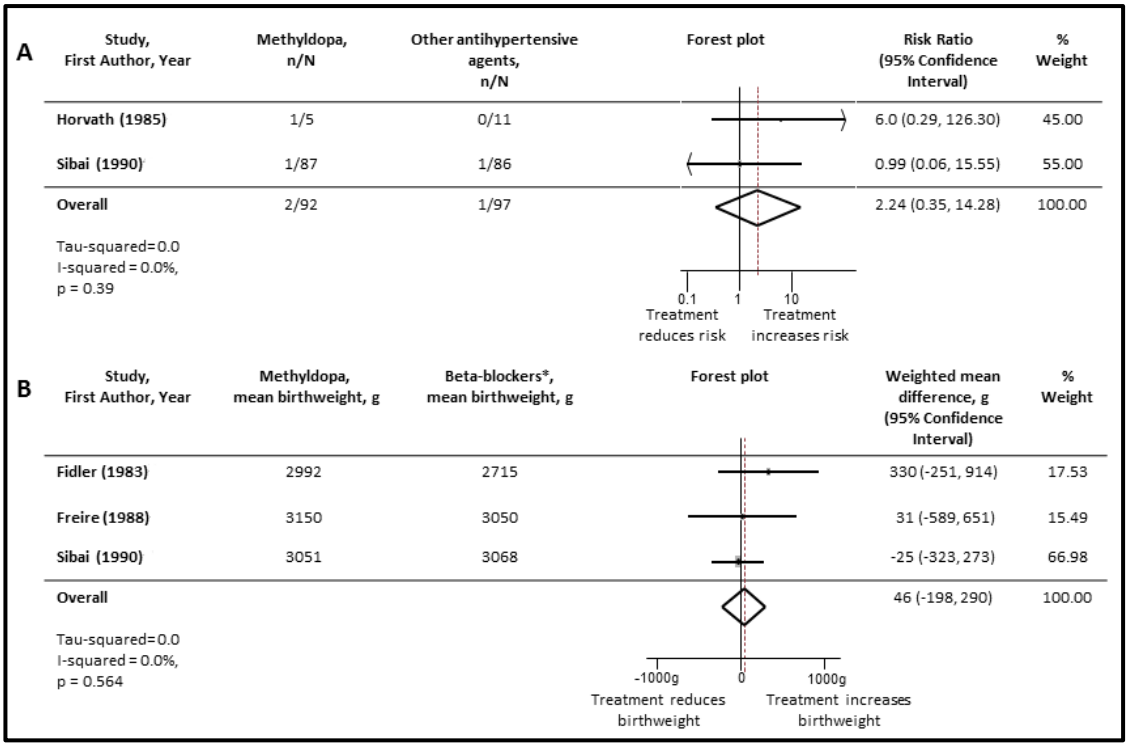


Figure 3.7 Perinatal outcomes: comparison of methyldopa versus other antihypertensive agents

A. *Stillbirth and neonatal death*
B. *Birthweight*

**Comparison made between methyldopa and beta-blockers as these were the only agents used in head-to-head trials reporting birthweight. Studies are listed in order of the year they were published. Antihypertensive agents used in each study are listed in Table 3.1. The number of participants experiencing a stillbirth/neonatal death in each treatment group are denoted as 'n', with the total number of participants with chronic hypertension in each study arm denoted as 'N'.*

3.5 Discussion

This is the largest systematic review of the evidence from randomised controlled trials to guide antihypertensive treatment specifically for chronic hypertension in pregnancy. Other systematic reviews have pooled results for chronic and gestational hypertension, but given the different aetiology and duration of treatment there are concerns with this approach. The reduction in the incidence of severe hypertension in pregnant women with chronic hypertension with the use of antihypertensive treatment is clinically important given the short and long-term associated maternal morbidity and mortality.[16,49,57,62,131,132] It is not possible at this time to recommend one agent over another for optimal blood pressure control, as there have only been three head-to-head randomised controlled trials enrolling 101 women that have examined this outcome.[264,265,275] No overall reduction in the risk of pre-eclampsia was seen with the use of antihypertensive treatment.

The paucity of data to guide selection of antihypertensive treatment for chronic hypertension in pregnancy is also highlighted. Only 15 randomised controlled trials totalling 1166 pregnancies meeting study eligibility criteria were identified and many of these were too small to address whether antihypertensive treatments reduce the risk of superimposed pre-eclampsia or influence other measures of perinatal morbidity. The only study published in the last 18 years by Vigil and colleagues compared three active treatment arms and antihypertensive treatments not recommended by most international guidelines as first line agents (amlodipine, furosemide and aspirin).[14] It could not be included in the meta-analysis given this design. This compares with many more trials and participants outside pregnancy; a recent systematic review of antihypertensive treatment (excluding pregnant participants) for the prevention of cardiovascular disease identified 123 randomised controlled trials including 613,815 participants.[299] Of the 15 studies reported here, only ten focused on chronic hypertension in pregnancy and the other five enrolled a mixed population of chronic and gestational hypertension, from which data for the participants with chronic hypertension were extracted. Given the changes in management of hypertension both inside and outside pregnancy, and that all of these trials were published between 1976 and 1998, optimal antihypertensive therapy for treating chronic hypertension in pregnancy warrants further investigation through large randomised controlled trials.

Antihypertensive use in pregnancy complicated by chronic hypertension does not increase the risk of stillbirth or neonatal death, no reduction in birthweight or increase in small for gestational age infants was seen, though heterogeneity was evident. This strengthens the finding that antihypertensive agents do not significantly affect perinatal morbidity; agent selection and higher than recommended dose are likely to account for the evidence from Butters and colleagues[154] who published data from a study of 29 participants randomised in the second trimester to atenolol or placebo.[154] Whilst it is evident the results of this study have influenced clinical practice,[14,16] this appears to be specific to this agent, or the very high doses that were used (up to 200 mg daily). Doses above 50 mg atenolol daily are not recommended and infrequently used nowadays for hypertension, as above this the dose-response curve is typically quite flat for blood-pressure lowering, with the maximum licensed dose for other indications being 100 mg daily. The primary results for this analysis have been presented without the inclusion of this study for these reasons. Von Dadelszen and colleagues (2000) also analysed with and without the data from the Butters study when examining the impact of

antihypertensive treatment on the risk of small for gestational age due to concerns over trial reporting.[129,300]

Ten of the 15 studies included in the meta-analysis evaluated agents that are no longer used for the routine management of hypertension in pregnancy in many countries (atenolol, acebutalol, oxprenolol, pindolol, bendroflumethiazide, hydrochlorothiazide, furosemide) or in the general non-pregnant population (ketanserin), accounting for about 45% of the participants studied. Whilst the labetalol is commonly used in pregnancy, not all beta-blockers can be considered equivalent. Labetalol is a racemate with alpha and non-selective beta antagonist activity (in a ratio of around one to three) for oral labetalol.[146,301] Oxprenolol, acebutalol and pindolol are more selective for beta-1 receptors than beta-2 receptors but are additionally partial agonists, possessing intrinsic sympathomimetic activity (resulting in less effect on reducing heart rate). Whilst licensed for hypertension, beta-blockers are no longer recommended as first line antihypertensive treatment, but are now regarded as fourth line agents for resistant hypertension in the general (non-pregnant) population.[1] The dose of bendroflumethiazide used (5-10 mg daily) is higher than that currently used for hypertension (2.5 mg daily). Therefore, a substantial proportion of the evidence for treatment of hypertension in pregnancy is based on outdated drugs and outdated doses. It is difficult to draw conclusions over the effect of antihypertensive agents on other maternal and perinatal outcomes. Meta-analysis of many maternal and fetal secondary outcomes was not possible due to a lack of reporting in the trials conducted to date. In addition, the planned adjustment for potential confounders such as body mass index was not possible due to inconsistent or absent reporting in the trial manuscripts. Further studies are needed to answer these questions and assess the potential impact of maternal characteristics such as obesity and other medical co-morbidities.

The Cochrane risk of bias assessment was high or unclear for all the studies included. This is primarily due to assignment of unclear risk of bias to many areas of study conduct and restrictions in the Cochrane tool. Many studies were open-label assigning them high risk of bias, which reflects the difficulties in blinding medication within pregnancy when blood pressure is dynamic and multiple dosing changes are required over a short time period. Additionally, the studies are not uniform in their reported outcome measures, which reflects the large time frame and variation in geographical setting of the studies. All studies included

are at least 18 years old and given the improvements in standards of clinical care in addition to standards of study conduct, there is the potential for substantial bias to be introduced.

Previous meta-analyses of the antihypertensive treatment of chronic hypertension in pregnancy are smaller than this study and have focussed on other interventions and outcomes.[257,302] The most recent of these was published in 2000. This study aimed to assess long-term treatment of chronic hypertension in pregnancy and the majority of trials did not provide sufficient detail to allow categorisation into mild or severe hypertension. In addition, a considerable portion of women will cross over from one group to the other making analysis problematic. A Cochrane review has been conducted on the use of antihypertensive treatment for 'mild to moderate' hypertension in pregnancy.[256] The authors conclude 'whether the reduction in the risk of severe hypertension is considered sufficient to warrant treatment is a decision that should be made by women in consultation with their obstetrician' and classed 'mild to moderate' hypertension as a systolic blood pressure up to and including 169 mmHg. In contrast, the Control of Hypertension in Pregnancy Study concludes that 'tight control' of blood pressure should be recommended to reduce the risk of short and long-term maternal morbidity given that this does not affect fetal or neonatal outcome adversely.[15,133] Subgroup analyses of those with chronic hypertension suggest a possible trend towards small for gestational age birthweight <10th centile (13.9% versus 19.7%; adjusted odds ratio 0.66, 95% confidence interval 0.44 to 1.00), however it is notable that in this subgroup the primary perinatal outcome was no different (odds ratio 1.08, 95% confidence interval 0.78 to 1.51). A post-hoc analysis of CHIPS found severe hypertension occurring in either intervention group (tight versus less-tight control) was associated with higher rates of pregnancy loss/neonatal unit admission and birthweight <10th centile,[133] suggesting a perinatal benefit to reducing the risk of severe hypertension. Additionally, those with severe hypertension in the less-tight control group were found to have an increased risk of serious maternal morbidity/mortality (odds ratio 3.74, 95% confidence interval 1.25 to 11.22).[133] Whilst some still question the need to treat hypertension before it reaches severe levels, the American Heart Association and the American Stroke Association recommend systolic blood pressure should be treated above the level of 150 mmHg to reduce the risk of stroke.[303] This recommendation is echoed in the findings of the UK triennial enquiry into maternal death, which found severe hypertension to be a factor in a significant proportion of hypertension related deaths.[49] Of note since this recommendation deaths from pre-eclampsia have fallen to less than 1 per million in the UK.[304]

The potential effects of 'less-tight control' on long-term maternal morbidity and mortality has recently been highlighted.[131,132] The Systolic blood Pressure INtervention Trial (SPRINT) stopped recruitment early due to the significant 25% reduction seen in a composite cardiovascular outcome (stroke, myocardial infarction and cardiac failure) with tighter control of systolic hypertension to a target of 120 mmHg rather than the standard treatment target of 140 mmHg; however this was coupled with a significant increase in serious adverse events such as hypotension, syncope and acute kidney injury.[305] Women of reproductive age with chronic hypertension are at substantially increased risk of cardiovascular morbidity and mortality.[306] Reducing the incidence of severe hypertension and maintaining tighter blood pressure control in pregnancy might contribute to lowering their long-term cardiovascular risk and warrants further investigation.

Earlier systematic reviews have focused on magnitude of initial hypertension rather than the underlying condition causing the hypertension. However, separating chronic and gestational hypertension, given the differing pathophysiological pathways and implications of treatment, allows focus on optimising treatment for each condition and is much more relevant to clinical practice.[151,256] Advances in the understanding of the mechanisms behind the exacerbation of hypertension in pregnancy and the associated increased risk of superimposed pre-eclampsia should be complemented with randomised controlled trials that examine how antihypertensive treatment may need to be tailored to the underlying pathophysiology. The International Society for the Study of Hypertension in Pregnancy guidelines classifying sub-types of hypertension in pregnancy have been refined over time and head-to-head randomised controlled trials comparing antihypertensive agents specifically for the treatment of chronic hypertension in pregnancy using these definitions are urgently needed.[21]

There is emerging evidence that tighter control of hypertension outside pregnancy reduces risks of long-term cardiovascular morbidity and mortality.[305] In light of the Control of Hypertension In Pregnancy Study data suggesting fetal safety with tighter control of hypertension, future research should focus on head-to-head randomised controlled trials of the most commonly used antihypertensive agents in current practice; this should include smaller trials to evaluate efficacy and larger trials to assess effectiveness of agent(s) for control of chronic hypertension in pregnancy. In addition, further consideration of the impact of maternal demographic factors should be considered such as body mass index and ethnicity. Outside pregnancy, calcium-channel blockers are recommended as first line antihypertensive

therapy for those of African or Caribbean family origin.[1] This is due to differing pathophysiological pathways causing hypertension that vary with ethnic origin.[78] It is possible that the efficacy of antihypertensive treatment is similarly affected by maternal ethnic background. This systematic review provides evidence to recommend women with chronic hypertension in pregnancy should receive antihypertensive treatment to reduce the incidence of severe hypertension and its associated maternal morbidity, without adversely affecting perinatal outcome.

In conclusion, antihypertensive treatment reduces the risk of severe hypertension in pregnant women with chronic hypertension. A considerable paucity of data exists from randomised controlled trials to guide choice of antihypertensive agent for chronic hypertension in pregnancy. Adequately powered head-to-head randomised controlled trials of the commonly used antihypertensive agents are required to inform prescribing.

CHAPTER 4 PREVALENCE OF ADVERSE PERINATAL OUTCOMES AND ASSOCIATED RISK FACTORS IN WOMEN WITH CHRONIC HYPERTENSION

4.1 Abstract

The objective of this study was to quantify the risk of adverse perinatal outcome in women with chronic hypertension compared to the general pregnant population, and to assess the impact of maternal characteristics on the risk of adverse perinatal outcome in women with chronic hypertension. Demographic and delivery data of women with chronic hypertension and singleton pregnancies from three obstetric units (2000-2014) were collated and compared with national maternity data. Then multivariable logistic regression models were used to calculate risk ratios (RR) for adverse perinatal outcome in women with chronic hypertension adjusted for maternal characteristics. The cohort included 4045 women (4481 pregnancies) with chronic hypertension. The incidence of adverse outcome was increased in the cohort compared with national maternity data: stillbirth 1.6% versus 0.6% (RR 2.83; 95% CI 2.25, 3.55), preterm birth <37 weeks 16% versus 8.9% (RR 2.16; 95% CI 2.00, 2.34), and birthweight <2500g 16% versus 6.6% (RR 2.63; 95% CI 2.43, 2.85). Maternal characteristics associated with an increased risk of adverse outcome included non-White ethnicity, advanced maternal age, primiparity, smoking, and deprivation. Black women, compared to White women, had the highest risk for all adverse outcomes: stillbirth: 3.1% versus 0.6% (adjusted RR 5.56; 95% CI 2.79, 11.1), preterm birth <37 weeks 21% versus 11% (aRR 1.70; 95% CI 1.43, 2.02), birthweight <3rd centile 16% versus 7.4% (aRR 2.07; 95% CI 1.71, 2.51). Non-White (particularly Black) ethnicity, deprivation, advanced maternal age, primiparity, and smoking all increase the risk of adverse perinatal outcome in women with chronic hypertension.

4.2 Introduction

The prevalence of chronic hypertension in pregnancy is rising due to increasing maternal age and the global obesity epidemic.[7,29,33,34,307] The current incidence of chronic hypertension in pregnancy is estimated at 3%, making it the most common pre-existing medical disorder that directly impacts maternal and fetal wellbeing.[29,32,45] The increased vascular resistance and decreased vascular compliance associated with chronic hypertension may cause maladaptation of the maternal circulation to the physiological demands of pregnancy.[110,308] Superimposed pre-eclampsia, stillbirth, fetal growth restriction, and preterm birth all occur more frequently in pregnancies complicated by chronic hypertension, compared with normotensive women.[8,29,50,53,54] This causes substantial maternal and perinatal morbidity and mortality and is therefore associated with increased healthcare cost.[309] The understanding of

mechanisms contributing to the increased risk of adverse outcomes among women with chronic hypertension is incomplete and the aetiology is likely to be multifactorial.

Previous cohort studies of women with chronic hypertension in pregnancy have focused on the maternal characteristics (age, body mass index, ethnicity) associated with an increased risk of superimposed pre-eclampsia. [43,45,47,54] However, increased adverse perinatal outcomes, independent of a diagnosis of superimposed pre-eclampsia, have been reported in women with chronic hypertension compared to the general pregnant population.[43,45,47,54] Maternal characteristics associated with adverse perinatal outcome in normotensive pregnancy have been established and include age,[310] obesity[6,311], smoking[312] and ethnicity[313-315]. Data examining the maternal characteristics associated with these increased risks in women with chronic hypertension in pregnancy are limited.[43,316-318]

Given the global changes in maternal demographics and its consequent effect on the prevalence of chronic hypertension in pregnancy, contemporaneous cohorts investigating incidence of adverse perinatal outcome and impact of maternal characteristics are needed to enable prioritisation of areas for further research. The objectives of this large multicentre cohort study were two-fold: firstly, to quantify the risk of adverse perinatal outcome in women with chronic hypertension and compare with the general pregnant population, and secondly, to assess the impact of maternal characteristics on the risk of adverse perinatal outcome in pregnancy complicated by chronic hypertension.

4.3 Methods

The cohort was collated from three obstetric units in the United Kingdom (UK): Guy's and St Thomas' National Health Service (NHS) Foundation Trust (London), St George's University Hospitals NHS Foundation Trust (London), and Central Manchester University Hospitals NHS Foundation Trust (Manchester). All deliveries after 20 weeks' gestation recorded on maternity databases between 2000 and 2014 with maternal history of chronic hypertension or a documented blood pressure greater than 140 mmHg systolic and/or 90 mmHg diastolic recorded before 20 weeks' gestation (as per the International Society for the Study of Hypertension in Pregnancy classification)[21] were extracted for analysis. Multifetal pregnancies were then excluded from the cohort due to a risk of confounding perinatal outcomes.[319] Demographic and delivery data were recorded for all the remaining singleton pregnancies complicated by chronic hypertension. Only pregnancies with a complete baseline demographic dataset (comprising maternal age, body mass index, parity, smoking, ethnicity, and deprivation

index) were included in the analysis. The size of the study was dictated by the earliest year maternal demographic and delivery data were recorded electronically at each centre.

Ethnicity (as recorded at antenatal booking) was assigned using four ethnic groups, White, Black, Asian, and Other, based on the grouping used by the UK Office for National Statistics.[320] Women of mixed ethnic origin were included in the group that they shared heritage with in the following order of priority: Black, Asian, White and Other. Socioeconomic status was classified using maternal postcode data, linked to lower super output area for calculation of indices of deprivation; participants were then categorised into the five groups with one being the least deprived and five being the most deprived.[321] Where the participant had no fixed abode they were included in deprivation index (Index of Multiple Deprivation) group five.

Birthweight centiles were calculated using birthweight centile charts (Gestation Related Optimal Weight (version 6.7.5.1 2014) and Intergrowth-21st (http://intergrowth21.ndog.ox.ac.uk/)).[322,323] The GROW customised birthweight centiles adjust for maternal height, maternal weight, maternal ethnicity, parity, gestation at delivery, infant sex and infant birthweight in its calculation.[322] The Intergrowth-21st birthweight centiles adjust for gestation at delivery, infant sex and infant birthweight.[323] Infants were then categorised into those with a birthweight less than the 10th centile and less than the 3rd centile (characterised as fetal growth restriction (FGR) by a recent Delphi consensus[65]). GROW birthweight centiles[322] were used in the primary analysis and Intergrowth-21st[323] for subsequent comparison. Preterm births (spontaneous and iatrogenic) were categorised as those born before 37 weeks' gestation and 34 weeks' gestation. Stillbirths were defined as infants born without signs of life after 20 weeks' gestation. Neonatal unit admission included infants requiring neonatal intensive care unit and/or special care baby unit admission.

Statistical Analysis

Means with standard deviation (SD) or medians with interquartile range (IQR) were calculated for continuous variables and numbers with percentages within the categories used for the regression models were calculated for maternal demographic characteristics and outcomes of the cohort with chronic hypertension and the NHS maternity statistics for England 2013-2014.[324] The mean and SD for maternal age from the NHS maternity dataset were estimated by replacing the age groups with their midranges. Comparison of maternal and perinatal

outcomes between the cohort and NHS maternity statistics was made by calculating risk ratios (RR) and associated 95% confidence intervals (95% CI).

Within the cohort of pregnancies complicated by chronic hypertension, unadjusted risk ratios and associated 95% CIs were calculated by generalised linear models using the statistical package Stata (version 14.1) for baseline demographic factors and subsequent perinatal outcomes (including stillbirth, preterm birth, neonatal unit admission, birthweight <10th centile, and birthweight <3rd centile). Adjusted risk ratios were then calculated using a multivariable regression model including demographic factors that could be explanatory or confounding in association with adverse perinatal outcome: ethnicity, deprivation index, maternal age, parity, body mass index, smoking history, and year of delivery. Allowance was made for women having more than one pregnancy within the cohort duration by adjusting the standard errors for clustering by hospital identification number. The validity of the model was confirmed by repeating the multivariable regression only including the significant risk factors for each perinatal outcome. In addition, a sensitivity analysis assessing the impact of centre on the results was conducted.

Further associations of adverse outcome and maternal characteristics were explored via chi-squared test or linear regression models. This included comparison of GROW and Intergrowth-21st birthweight centiles and their impact on the study findings. Investigation of possible confounding included assessing the impact of centre of delivery on each perinatal outcome.

The study was reported in line with STROBE guidance for observational studies.[325]

4.4 Results

Data from 4481 singleton pregnancies in 4045 women with chronic hypertension between 2000 and 2014 were included in the analysis. The flow diagram of participants is shown in Figure 4.1. Only pregnancies with all demographic characteristics required for the multivariate regression model were included in the final analysis (86% of singleton pregnancies identified). The most common missing data point was body mass index accounting for 13% of pregnancies excluded from the analysis with the majority of these in the earliest years of the dataset. Sixteen postcodes could not be linked to lower super output areas; these participants were also excluded from the analysis. Thirteen women had no fixed abode and were included in deprivation index group five.

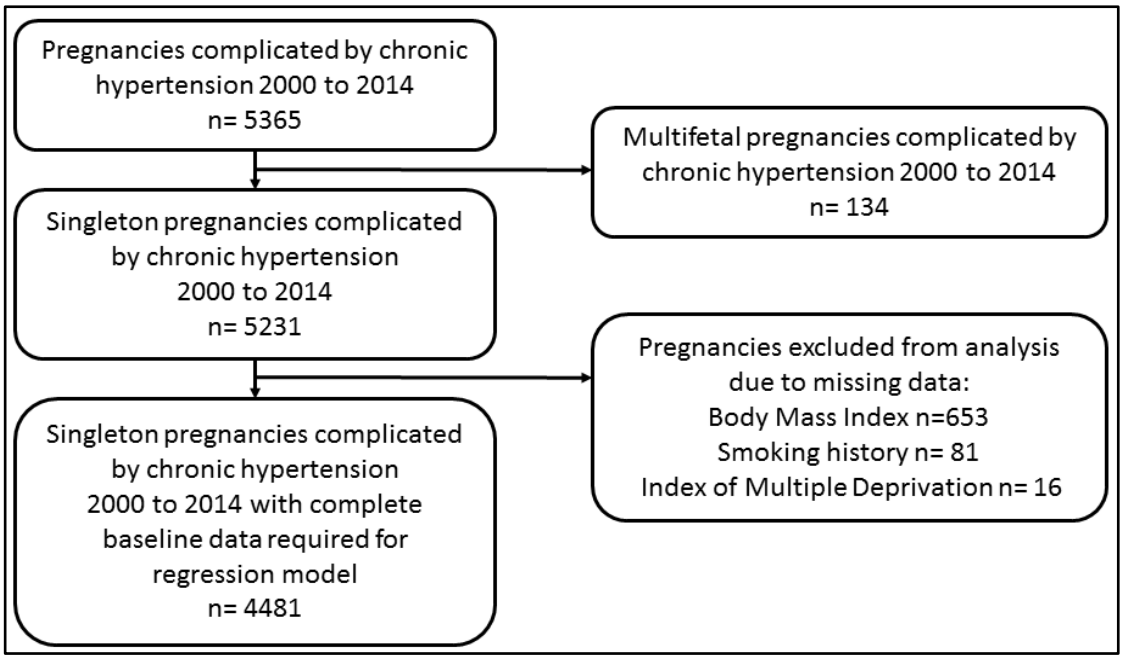


Figure 4.1 Flow diagram of identification of the study cohort

Comparison of the cohort of pregnancies with chronic hypertension to national maternity statistics

The summary demographic characteristics of the cohort and the NHS maternity statistics for 2013 to 2014 are provided in Table 4.1. There was a higher proportion of Black women in the cohort with chronic hypertension compared with the general pregnant population (36% versus 4.8%; p <0.001) and the proportion of women aged 40 years or older was also higher (13% versus 3.9%; p <0.001).[324] There were a greater number of pregnancies included in the cohort from 2010 onwards as maternity records from Central Manchester University Hospitals NHS Foundation Trust were not available before this date.

Table 4.1 Demographic characteristics of the cohort (2000-2014)

Maternal Characteristic	Pregnancies with chronic hypertension n=4481	NHS maternity statistics England 2013 to 2014 n= 646,904	Significance
Age at delivery, years mean (SD)	33 (5.8)	30 (5.5)	P <0.001
<25	384 (8.5%)	136,420 (21%)	
25-29.9	762 (17%)	181,017 (30%)	
30-34.9	1454 (32%)	194,398 (30%)	
35-39.9	1299 (29%)	100,339 (16%)	
≥40	582 (13%)	24,953 (3.9%)	
Body Mass Index, kg/m^2 mean (SD)	28.4 (6.4)		
<25	1463 (33%)		
25-29.9	1332 (30%)		
30-34.9	945 (21%)		
≥35	741 (17%)		
Parity*			
Nulliparous	2112 (47%)	164,774 (37%)	P <0.001
Multiparous	2369 (53%)	283,952 (63%)	
Non-smoker	4169 (93%)		
Smoker	312 (7%)		
Ethnicity*			
White	2122 (47%)	463,049 (72%)	P <0.001
Black	1601 (36%)	31,176 (4.8%)	
Asian	379 (8.5%)	69,734 (11%)	
Other	379 (8.5%)	33,606 (5.2%)	
Deprivation Index			
1 (least deprived)	350 (7.8%)	94,245 (15%)	P <0.001
2	462 (10%)	100,495 (16%)	
3	953 (21%)	117,629 (18%)	
4	1403 (31%)	143,982 (22%)	
5 (most deprived)	1313 (29%)	177,252 (27%)	
Year of pregnancy			
2000-2004	836 (19%)		
2005-2009	1598 (36%)		
2010-2014	2047 (46%)		
Centre			
Guy's and St Thomas' NHS Foundation Trust	2016 (45%)		
St George's University Hospitals NHS Foundation Trust	2029 (45%)		
Central Manchester University Hospitals NHS Foundation Trust	436 (9.7%)		

**30% of the parity data and 7% of the ethnicity data for the NHS maternity statistics was unknown. For all continuous variables, the categories used in the regression model are additionally shown.*

All major adverse perinatal outcomes, with the exception of macrosomia, were significantly higher in women with chronic hypertension compared to the general pregnant population: stillbirth, birthweight <2500g, preterm birth <37 weeks' gestation, iatrogenic delivery, and Caesarean delivery (Table 4.2). The stillbirth rate was nearly three times that seen in the general pregnant population (RR 2.83; 95% CI 2.25 to 3.55). The risk of preterm birth before 37 completed weeks' gestation was more than double in the cohort of women with chronic hypertension (RR 2.16; 95% CI 2.00 to 2.34). The proportion of babies born weighing <2500g was more than twice as high in the cohort of women with chronic hypertension (RR 2.63; 95% CI 2.43 to 2.85), but the proportion of babies born >4500g was comparable between the cohort and national data. In addition, higher rates of induction of labour and caesarean section birth were found in the cohort with chronic hypertension (Table 4.2).

Table 4.2 Maternal and perinatal outcomes

	Chronic Hypertensive Pregnancies n=4481	NHS maternity statistics England, 2013 to 2014 n=531,194	Risk ratio (95% CI)
Maternal Outcomes			
Gestation at delivery, weeks median (IQR)	39.3 (38.0 to 40.4)		
Onset of labour			
Spontaneous	1832 (40.8%)	319,146 (60.1%)	
Induction	1471 (32.8%)	100,913 (19.0%)	2.53 (2.38 to 2.69)*
Pre-labour caesarean section	1007 (22.5%)	68,103 (12.8%)	
Mode of delivery†			
Spontaneous vaginal delivery	2152 (48.0%)	319,238 (60.1%)	
Instrumental delivery	580 (12.9%)	67,312 (12.7%)	1.28 (1.17 to 1.40)
Caesarean section delivery	1749 (39%)	135,516 (25.5%)	1.82 (1.71 to 1.93)
Elective caesarean section	611 (13.6%)	56,675 (10.7%)	
Emergency caesarean section	1138 (25.4%)	78,841 (14.8%)	
Estimated blood loss, ml, mean (SD)	500 (420)		
High dependency unit admission‡	417 (10.5%)		
Fetal outcomes			
Stillbirth	72 (1.6%)	3125 (0.6%)§	2.83 (2.25 to 3.55)
Preterm birth			
<37 weeks	701 (15.6%)	41,631 (7.8%)	2.16 (2.00 to 2.34)
<34 weeks	305 (6.8%)		
Birthweight, g, median (IQR)	3230 (2780 to 3630)		
<2500g	708 (15.8%)	36,598 (6.6%)‖	2.63 (2.43 to 2.85)
>4500g	68 (1.5%)	9087 (1.6%)‖	0.93 (0.73 to 1.18)
Birthweight centile			
<10th centile	1047 (23.4%)		
<3rd centile	499 (11.1%)		
Neonatal unit admission	413 (9.2%)		

**Risk ratio calculated for iatrogenic onset of labour compared with spontaneous, †data reported for n=521,346, ‡data regarding maternal high dependency unit admission was only available for 79% of the cohort, §data reported for n=552,036, ‖ data reported for n=555,445, IQR= interquartile range, SD= standard deviation*

Multivariable regression model analysis of risk factors contributing to adverse perinatal outcome in the cohort of pregnancies complicated by chronic hypertension

Using stillbirth as an important perinatal endpoint, the impact of maternal characteristics was assessed in a multivariable regression model. The only maternal characteristics remaining significant in the adjusted model were Black and Asian ethnicity. Black women had a risk ratio of 5.56 (95% CI 2.79 to 11.09) of having a stillbirth compared to White women, and Asian women had risk ratio of 3.03 (95% CI 1.11 to 8.28) compared to White women (Table 4.3).

Table 4.3 Effect of baseline characteristics on risk of stillbirth

Risk category	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)
Age, years		
<25	0.76 (0.29 to 1.97)	0.60 (0.22 to 1.62)
25 to 29.9	0.53 (0.23 to 1.23)	0.46 (0.20 to 1.07)
30 to 34.9	1.00 (Reference)	
35 to 39.9	0.99 (0.56 to 1.74)	0.91 (0.51 to 1.61)
≥40	1.30 (0.67 to 2.52)	1.07 (0.54 to 2.13)
BMI, kg/m^2		
<25	1.00 (Reference)	
25 to 29.9	1.21 (0.66 to 2.25)	0.92 (0.49 to 1.72)
30 to 34.9	1.47 (0.77 to 2.78)	1.00 (0.52 to 1.92)
≥35	1.45 (0.73 to 2.88)	1.03 (0.51 to 2.08)
Nulliparity	1.00 (0.63 to 1.59)	1.56 (0.94 to 2.60)
Multiparity	1.00 (Reference)	
Non-Smoker	1.00 (Reference)	
Smoker	0.38 (0.09 to 1.55)	0.53 (0.12 to 2.20)
Ethnicity		
White	1.00 (Reference)	
Black	5.41* (2.89 to 10.1)	5.56* (2.79 to 11.09)
Asian	2.80* (1.06 to 7.40)	3.03* (1.11 to 8.28)
Other	2.33 (0.83 to 6.56)	2.28 (0.81 to 6.42)
Year of delivery		
2000 to 2004	1.01 (0.54 to 1.87)	1.06 (0.57 to 1.98)
2005 to 2009	0.90 (0.54 to 1.51)	0.95 (0.57 to 1.98)
2010 to 2014	1.00 (Reference)	
Deprivation Index		
1 to 3	1.00 (Reference)	
4	1.72 (0.96 to 3.09)	1.23 (0.69 to 2.18)
5 (most deprived)	1.91* (1.07 to 3.42)	1.31 (0.60 to 2.12)

** Results reaching statistical significance p<0.05*

When the risks were calculated for birthweight <3rd centile, women aged 40 years or older (RR 1.53; 95% CI 1.09 to 2.16), women who smoked (RR 1.53; 95% CI 1.15 to 2.04) and women of Black (RR 2.07; 95% CI 1.71 to 2.51), Asian (RR 1.69; 95% CI 1.24 to 2.30) or Other ethnicity (RR 1.70, 95% CI 1.26 to 2.31) were at significantly increased risk (Table 4.4). Baseline characteristics significantly increasing the risk of birthweight <10th centile in the adjusted model included being aged 40 years or older (RR 1.34; 95% CI 1.06 to 1.69), nulliparity (RR 1.16; 95% CI 1.03 to1.30), smoking (RR 1.52; 95% CI 1.28 to 1.81), living in an area of greatest deprivation (RR 1.20; 95% CI 1.04 to 1.38), and Black ethnicity (RR 1.64; 95% CI 1.45 to 1.87) (Table 4.5).

Table 4.4 Effect of baseline characteristics on risk of birthweight <3rd centile

Risk category	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)	Adjusted Risk Ratio- significant predictors only (95% CI)
Age, years			
<25	1.03 (0.74 to 1.43)	0.89 (0.64 o 1.25)	
25 to 29.9	0.97 (0.74 to 1.26)	0.92 (0.70 to 1.19)	
30 to 34.9	1.00 (Reference)		
35 to 39.9	1.07 (0.86 to 1.33)	1.05 (0.84 to 1.31)	
≥40	1.64* (1.29 to 2.09)	1.51* (1.18 to 1.93)	1.53* (1.09 to 2.16)
BMI, kg/m^2			
<25	1.00 (Reference)		
25 to 29.9	1.29* (1.04 to 1.60)	1.11 (0.89 to 1.38)	
30 to 34.9	1.35* (1.07 to 1.70)	1.07 (0.84 to 1.37)	
≥35	1.14 (0.87 to 1.49)	0.90 (0.68 to 1.20)	
Nulliparity	0.96 (0.81 to 1.13)	1.19 (0.99 to 1.42)	
Multiparity	1.00 (Reference)		
Non-Smoker	1.00 (Reference)	-	
Smoker	1.32 (0.99 to 1.75)	1.57* (1.18 to 2.09)	1.53* (1.15 to 2.04)
Ethnicity			
White	1.00 (Reference)	-	
Black	2.10* (1.73 to 2.53)	2.04* (1.66 to 2.52)	2.07* (1.71 to 2.51)
Asian	1.63* (1.20 to 2.23)	1.67* (1.22 to 2.29)	1.69* (1.24 to 2.30)
Other	1.70* (1.26 to 2.31)	1.65* (1.22 to 2.24)	1.70* (1.26 to 2.31)
Year of delivery			
2000 to 2004	0.92 (0.73 to 1.16)	0.95 (0.76 to 1.19)	
2005 to 2009	0.84 (0.69 to 1.01)	0.87 (0.72 to 1.05)	
2010 to 2014	1.00 (Reference)		
Deprivation Index			
1 to 3	1.00 (Reference)	-	
4	1.35* (1.10 to 1.66)	1.15 (0.94 to 1.42)	
5 (most deprived)	1.46* (1.19 to 1.79)	1.14 (0.92 to 1.42)	

*CI= confidence interval * Results reaching statistical significance p<0.05.*

Table 4.5 Effect of baseline characteristics on risk of birthweight <10th centile

Risk category	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)	Adjusted Risk Ratio- significant predictors only (95% CI)
Age, years			
<25	1.08 (0.88 to 1.33)	0.95 (0.77 to 1.17)	-
25 to 29.9	1.02 (0.87 to 1.20)	0.96 (0.82 to 1.13)	-
30 to 34.9	1.00 (Reference)		-
35 to 39.9	1.05 (0.91 to 1.21)	1.03 (0.90 to 1.19)	-
≥40	1.36* (1.15 to 1.59)	1.26* (1.07 to 1.49)	1.34* (1.06 to 1.69)
BMI, kg/m^2			
<25	1.00 (Reference)		-
25 to 29.9	1.13 (0.98 to 1.30)	1.01 (0.88 to 1.16)	-
30 to 34.9	1.16 (0.99 to 1.35)	0.99 (0.85 to 1.15)	-
≥35	1.15 (0.97 to 1.35)	0.96 (0.81 to 1.14)	-
Nulliparity	0.99 (0.89 to 1.10)	1.15* (1.03 to 1.29)	1.16* (1.03 to 1.30)
Multiparity	1.00 (Reference)		
Non-Smoker	1.00 (Reference)	-	-
Smoker	1.39* (1.16 to 1.66)	1.53* (1.28 to 1.81)	1.52* (1.28 to 1.81)
Ethnicity			
White	1.00 (Reference)	-	-
Black	1.68* (1.49 to 1.89)	1.65* (1.45 to 1.88)	1.64* (1.45 to 1.87)
Asian	1.17 (0.94 to 1.46)	1.21 (0.97 to 1.51)	-
Other	1.20 (0.97 to 1.49)	1.18 (0.95 to 1.46)	-
Year of delivery			
2000 to 2004	0.96 (0.83 to 1.11)	0.97 (0.84 to 1.12)	
2005 to 2009	0.90 (0.79 to 1.01)	0.92 (0.82 to 1.04)	-
2010 to 2014	1.00 (Reference)		
Deprivation Index			
1 to 3	1.00 (Reference)	-	-
4	1.21* (1.06 to 1.39)	1.08 (0.94 to 1.25)	-
5 (most deprived)	1.41* (1.24 to 1.61)	1.19* (1.04 to 1.37)	1.20* (1.04 to 1.38)

*CI= confidence interval * Results reaching statistical significance p<0.05.*

Factors increasing the risk of preterm birth before 37 weeks' gestation included: being aged 40 years or older (RR 1.52; 95% CI 1.13 to 2.05), nulliparity (RR 1.17; 95% CI 1.01 to 1.35), living in area of greatest deprivation (RR 1.42; 95% CI 1.18 to 1.70), and Black or Asian ethnicity (RR 1.70; 95% CI 1.43 to 2.01 and RR 1.82; 95% CI 1.41 to 2.35 respectively) (Table 4.6). When the analysis was repeated assessing the risk of preterm birth before 34 weeks' gestation, only women of Black (RR 2.69; 95% CI 2.03 to 3.55), Asian (RR 2.48; 95% CI 1.69 to 3.66) and Other ethnic groups (RR 1.69; 95% CI 1.07 to 2.68), and women living in the most deprived areas (RR

1.39; 95% CI 1.05 to 1.86) were at significantly increased risk (Table 4.7). In this cohort, where 15.6% of women delivered preterm, 3.2% followed spontaneous labour whilst 12.4% were iatrogenic. No ethnic difference was seen amongst the spontaneous preterm births, but the proportion of Black versus White women giving birth before 37 weeks' gestation through iatrogenic delivery was 17% versus 7.9% (p<0.0001).

Table 4.6 Effect of baseline characteristics on risk of preterm birth <37 weeks' gestation

Risk category	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)	Adjusted Risk Ratio-significant predictors only (95% CI)
Age, years			
<25	1.01 (0.77 to 1.33)	0.86 (0.65 to 1.14)	
25 to 29.9	0.90 (0.72 to 1.13)	0.83 (0.67 to 1.04)	
30 to 34.9	1.00 (Reference)		
35 to 39.9	1.16 (0.97 to 1.38)	1.13 (0.94 to 1.35)	
≥40	1.45* (1.18 to 1.77)	1.35* (1.09 to 1.66)	1.52* (1.13 to 2.05)
BMI, kg/m^2			
<25	1.00 (Reference)		
25 to 29.9	1.22* (1.02 to 1.45)	1.06 (0.89 to 1.27)	
30 to 34.9	1.28* (1.05 to 1.55)	1.05 (0.86 to 1.28)	
≥35	1.27* (1.03 to 1.57)	1.06 (0.86 to 1.32)	
Nulliparity	0.94 (0.82 to 1.08)	1.19* (1.02 to 1.38)	1.17* (1.01 to 1.35)
Multiparity	1.00 (Reference)		
Non-Smoker	1.00 (Reference)	-	
Smoker	1.09 (0.84 to 1.42)	1.26 (0.97 to 1.63)	
Ethnicity			
White	1.00 (Reference)	-	
Black	1.88* (1.61 to 2.20)	1.70* (1.43 to 2.02)	1.70* (1.43 to 2.01)
Asian	1.83* (1.42 to 2.35)	1.86* (1.44 to 2.40)	1.82* (1.41 to 2.35)
Other	1.26 (0.95 to 1.66)	1.21 (0.91 to 1.60)	
Year of delivery			
2000 to 2004	1.04 (0.86 to 1.25)	1.11 (0.92 to 1.33)	
2005 to 2009	0.98 (0.84 to 1.15)	1.04 (0.89 to 1.21)	
2010 to 2014	1.00 (Reference)		
Deprivation Index			
1 to 3	1.00 (Reference)	-	
4	1.44* (1.20 to 1.72)	1.30* (1.08 to 1.56)	1.30* (1.09 to 1.56)
5 (most deprived)	1.67* (1.41 to 1.98)	1.43* (1.19 to 1.71)	1.42* (1.18 to 1.70)

*CI= confidence interval * Results reaching statistical significance p<0.05*

Table 4.7 Effect of baseline characteristics on risk of premature birth <34 weeks' gestation

Risk category	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)	Adjusted Risk Ratio- significant predictors only (95% CI)
Age, years			
<25	1.22 (0.81 to 1.84)	1.00 (0.65 to 1.54)	-
25 to 29.9	0.94 (0.66 to 1.34)	0.84 (0.59 to 1.20)	-
30 to 34.9	1.00 (Reference)		-
35 to 39.9	1.19 (0.89 to 1.58)	1.13 (0.84 to 1.51)	-
≥40	1.57* (1.14 to 2.19)	1.39 (0.99 to 1.94)	-
BMI, kg/m^2			
<25	1.00 (Reference)		-
25 to 29.9	1.11 (0.84 to 1.47)	0.90 (0.68 to 1.19)	-
30 to 34.9	1.26 (0.93 to 1.47)	0.93 (0.69 to 1.26)	-
≥35	1.04 (0.74 to 1.47)	0.79 (0.56 to 1.12)	-
Nulliparity	0.92 (0.74 to 1.14)	1.18 (0.94 to 1.49)	-
Multiparity	1.00 (Reference)		-
Non-Smoker	1.00 (Reference)	-	-
Smoker	1.04 (0.67 to 1.60)	1.34 (0.87 to 2.07)	-
Ethnicity			
White	1.00 (Reference)	-	-
Black	2.97* (2.28 to 3.87)	2.81* (2.10 to 3.76)	2.69* (2.03 to 3.55)
Asian	2.58* (1.75 to 3.79)	2.67* (1.79 to 3.96)	2.48* (1.69 to 3.66)
Other	1.77* (1.12 to 2.79)	1.68* (1.06 to 2.68)	1.69* (1.07 to 2.68)
Year of delivery			
2000 to 2004	0.82 (0.60 to 1.13)	0.86 (0.62 to 1.18)	-
2005 to 2009	0.95 (0.75 to 1.21)	0.99 (0.78 to 1.26)	-
2010 to 2014	1.00 (Reference)		-
Deprivation Index			
1 to 3	1.00 (Reference)	-	-
4	1.54* (1.16 to 2.06)	1.24 (0.93 to 1.66)	-
5 (most deprived)	1.94* (1.48 to 2.56)	1.41* (1.06 to 1.88)	1.39* (1.05 to 1.86)

*CI= confidence interval * Results reaching statistical significance p<0.05.*

Neonatal unit admission was associated with Black, Asian and Other ethnicity compared to White (RR 1.55; 95% CI 1.25 to 1.93, RR 1.58; 95% CI 1.12 to 2.23, and RR 1.46; 95% CI 1.06 to 2.04 respectively), and nulliparity compared to multiparity (RR 1.32; 95% CI 1.08 to 1.61) (Table 4.8). Year of delivery also affected the risk of neonatal unit admission with babies born between 2000-2004 and 2005-2009 at greater risk than those born between 2010-2014 (RR 1.35; 95% CI 1.05 to 1.74, and RR 1.30; 95% CI 1.06 to 1.60 respectively).

Table 4.8 Effect of baseline characteristics on risk of neonatal unit admission

Risk category	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)	Adjusted Risk Ratio- significant predictors only (95% CI)
Age, years			
<25	1.17 (0.82 to 1.66)	0.98 (0.68 to 1.41)	-
25 to 29.9	1.04 (0.78 to 1.38)	0.97 (0.73 to 1.29)	-
30 to 34.9	1.00 (Reference)		-
35 to 39.9	1.14 (0.89 to 1.45)	1.16 (0.91 to 1.48)	-
≥40	1.40* (1.05 to 1.86)	1.42* (1.06 to 1.90)	1.38 (0.93 to 2.04)
BMI, kg/m^2			
<25	1.00 (Reference)		-
25 to 29.9	1.07 (0.84 to 1.36)	1.01 (0.79 to 1.28)	-
30 to 34.9	1.20 (0.93 to 1.55)	1.13 (0.87 to 1.47)	-
≥35	1.19 (0.91 to 1.57)	1.13 (0.84 to 1.51)	-
Nulliparity	1.14 (0.95 to 1.37)	1.36* (1.11 to 1.66)	1.32* (1.08 to 1.61)
Multiparity	1.00 (Reference)		
Non-Smoker	1.00 (Reference)	-	-
Smoker	1.17 (0.83 to 1.65)	1.29 (0.92 to 1.82)	-
Ethnicity			
White	1.00 (Reference)	-	-
Black	1.53* (1.24 to 1.88)	1.48* (1.18 to 1.86)	1.55* (1.25 to 1.93)
Asian	1.48* (1.05 to 2.09)	1.58* (1.12 to 2.24)	1.58* (1.12 to 2.23)
Other	1.45* (1.04 to 2.02)	1.44* (1.03 to 2.01)	1.46* (1.05 to 2.04)
Year of delivery			
2000 to 2004	1.29* (1.01 to 1.66)	1.36* (1.05 to 1.76)	1.35* (1.05 to 1.74)
2005 to 2009	1.28* (1.04 to 1.57)	1.33* (1.07 to 1.63)	1.30* (1.06 to 1.60)
2010 to 2014	1.00 (Reference)		
Deprivation Index			
1 to 3	1.00 (Reference)	-	-
4	1.29* (1.03 to 1.61)	1.20 (0.95 to 1.52)	-
5 (most deprived)	1.22* (0.97 to 1.54)	1.12 (0.88 to 1.43)	-

*CI= confidence interval * Results reaching statistical significance p<0.05.*

A sensitivity analysis assessing the impact of centre on the significant findings of the regression model was conducted in two ways: including centre in the regression model and repeating the regression model including only the data from women who delivered their babies in the last five years of the study (as data from Central Manchester University Hospitals NHS Foundation Trust was only available for this time period). Although there were differences in the incidence of each adverse outcome at each centre, the maternal characteristics that significantly

increased the risk of each adverse outcome did not change when centre was included in the regression model.

In the second sensitivity analysis, the reduction in the number of participants included due to restriction of the timeframe reduced power, and led to the loss of some of the significant results. However, the characteristics associated with the greatest increased risk of adverse outcome remained significant. Non-White ethnicity, living in an area of greater deprivation, smoking and primiparity were all associated with and increased risk of adverse outcome in this model.

A summary of all the significant adjusted risk ratios and related confidence intervals for the maternal characteristics associated with adverse perinatal outcome in women with chronic hypertension was collated (Table 4.10). Given the strong association of ethnicity with adverse perinatal outcome, the prevalence, adjusted risk ratios, and related confidence intervals were additionally compared in Table 4.11 for all perinatal outcomes analysed and stratified by ethnic group.

Table 4.9 Adjusted risk ratios (95% confidence intervals) of significant maternal characteristics associated with adverse perinatal outcomes in women with chronic hypertension

Perinatal outcome	Black versus White women	Asian versus White women	Maternal age >40 years versus <25 years	Smokers versus non-smokers	Primip versus multip	Deprivation Index group 5* versus 1 to 3
Stillbirth	5.56 (2.79 to 11.09)	3.03 (1.11 to 8.28)				
Birthweight <10th centile	1.64 (1.45 to 1.87)		1.34 (1.06 to 1.69)	1.52 (1.28 to 1.81)	1.16 (1.03 to 1.30)	1.20 (1.04 to 1.38)
Birthweight <3rd centile	2.07 (1.71 to 2.51)	1.69 (1.24 to 2.30)	1.53 (1.09 to 2.16)	1.53 (1.15 to 2.04)		
Preterm <37 weeks	1.70 (1.43 to 2.01)	1.82 (1.41 to 2.35)	1.52 (1.13 to 2.05)		1.17 (1.01 to 1.35)	1.42 (1.18 to 1.70)
Preterm <34 weeks	2.69 (2.03 to 3.55)	2.48 (1.69 to 3.66)				1.39 (1.05 to 1.86)
Neonatal unit admission	1.55 (1.25 to 1.93)	1.58 (1.12 to 2.23)			1.32 (1.08 to 1.61)	

**Deprivation index group 5 is associated with the greatest deprivation.*

Table 4.10 Adverse perinatal outcomes stratified by ethnic group

Perinatal outcome	White n=2122 Prevalence % (Referent)	Black n=1601 Prevalence % Adjusted risk ratio (95% CI)	Asian n=379 Prevalence % Adjusted risk ratio (95% CI)	Other n=379 Prevalence % Adjusted risk ratio (95% CI)
Stillbirth	0.6%	3.1% 5.56* (2.79 to 11.1)	1.6% 3.03* (1.11 to 8.28)	1.3% 2.28 (0.81 to 6.42)
Birthweight <10th centile	18%	31% 1.65* (1.45 to 1.88)	22% 1.21 (0.97 to 1.51)	22% 1.18 (0.95 to 1.46)
Birthweight <3rd centile	7.4%	16 % 2.07* (1.71 to 2.51)	12% 1.69* (1.24 to 2.30)	13% 1.70* (1.26 to 2.31)
Preterm <37 weeks	11%	21% 1.70* (1.43 to 2.02)	20% 1.86* (1.44 to 2.40)	14% 1.21 (0.91 to 1.60)
Preterm <34 weeks	3.6%	11% 2.81* (2.10 to 3.76)	9.2% 2.67* (1.79 to 3.96)	6.8% 1.68* (1.06 to 2.68)
Neonatal unit admission	7.7%	12% 1.55* (1.25 to 1.93)	11% 1.58* (1.12 to 2.23)	11% 1.46* (1.05 to 2.04)

** Results reaching statistical significance p<0.05.*

Further investigation into potential aetiology underpinning disparity in outcome within the cohort of pregnancies complicated by chronic hypertension

Investigation of a surrogate for severity of maternal disease was conducted by comparing the proportion of mothers admitted to the high dependency unit or intensive care unit after birth. Black mothers versus White mothers were more likely to require high level care after birth, 14% versus 8.2% (odds ratio 1.83; 95% CI 1.46 to 2.29).

Of stillborn babies, 77% had a birthweight <10th centile and 63% had a birthweight <3rd centile. Most stillbirths occurred before 37 weeks' gestation (93%). No impact of ethnicity on the proportion of infants with birthweight <10th centile or the gestation at delivery was found amongst the stillbirths. Within the entire cohort, the proportion of neonates with birthweight <3rd centile was higher amongst those born preterm (54% of births before 34 weeks' gestation and 19% of births 34 to 37 weeks' gestation) compared to 6.9% of births from 37 weeks' gestation (Figure 4.2). Just over half the infants requiring neonatal admission had birthweights below the 10th centile and 40% of infants requiring neonatal unit admission had birthweight <3rd centile.

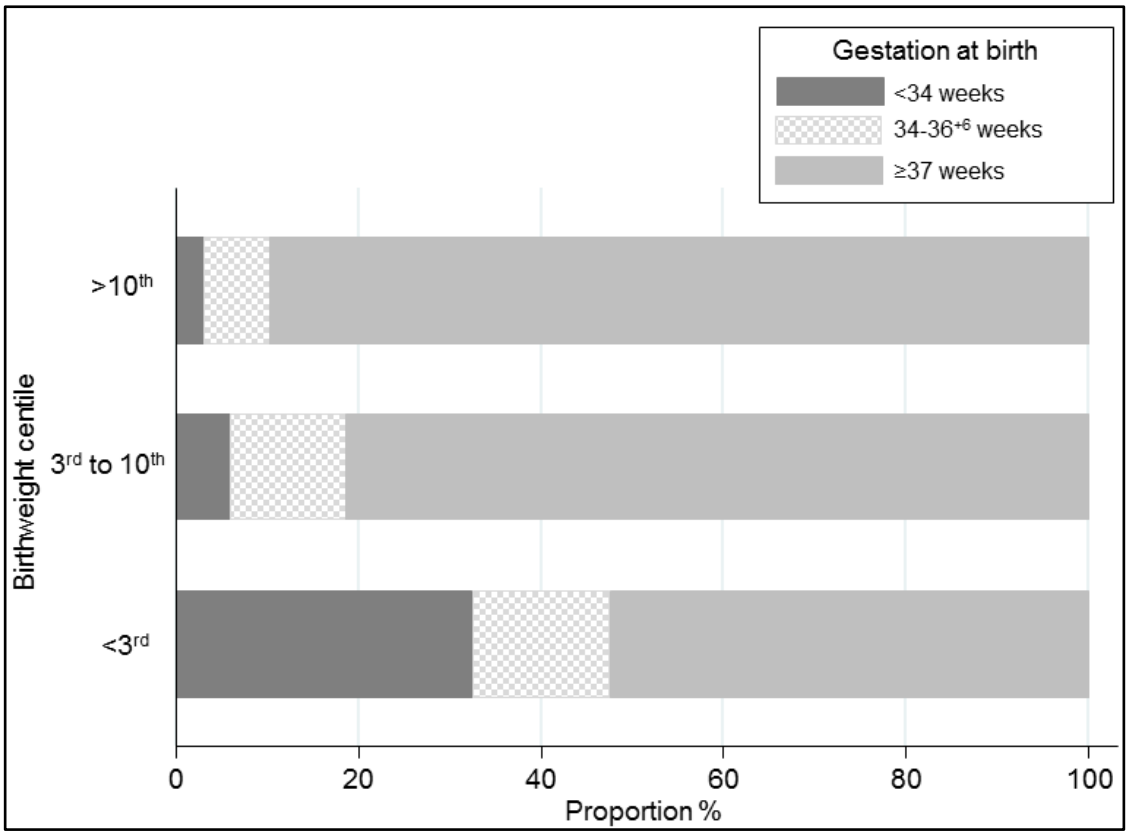


Figure 4.2 Comparison of gestation at birth and birthweight centile category

Further investigation of the importance of ethnicity within birthweight centile calculation was assessed by comparing the Intergrowth-21st birthweight centiles, which do not include maternal ethnicity within its adjustment , with the GROW birthweight centiles.[322,323] The proportion of infants classed as <3rd birthweight centile was 11% using the GROW versus 5.1% using Intergrowth-21st birthweight centiles; those with birthweight <10th centile were 23% versus 13% respectively. No infants classed as birthweight <3rd centile by Intergrowth-21st but not by GROW were admitted to the neonatal care unit; however, 47 infants (12%) requiring neonatal unit admission were classed as birthweight <3rd centile by GROW but birthweight >10th by Intergrowth-21st.The sensitivity and specificity for infants requiring neonatal unit admission were 40% and 93% for those with birthweight <3rd centile calculated using GROW, compared to 16% and 96% respectively for those with birthweight <3rd centile calculated using Intergrowth-21st.

4.5 Discussion

This large contemporary cohort study demonstrates that pregnancy complicated by chronic hypertension is associated with an increased risk of all adverse perinatal outcomes compared to recent national UK data. Maternal characteristics associated with an increased the risk of

adverse perinatal outcome in women with chronic hypertension have been identified. Non-White (especially Black) ethnicity, advanced maternal age, smoking status, primiparity and deprivation all have an impact on the perinatal complications to differing extents. Women of Black ethnicity with chronic hypertension are at significantly greater risk of all adverse perinatal outcomes than White women with chronic hypertension in pregnancy. Women of Asian and Other ethnicities are also at increased risk, but to a lesser extent. These findings underline the importance of prioritising research into optimising the management of chronic hypertension in pregnancy.

It is striking that Black ethnicity was consistently associated with the highest increased risk for all adverse outcomes compared with other baseline characteristics in women with chronic hypertension in pregnancy, even after controlling for deprivation, maternal age, BMI and smoking. The explanation for this increased risk is likely to be multifactorial with biological and non-biological factors contributing. Women with chronic hypertension who were of Black (versus White) ethnicity had a more than a five-fold increase in stillbirth risk which was similar among women with chronic hypertension of White ethnicity and the UK maternity population (0.6%).[34] A disparity in incidence of stillbirth in women born in African and Caribbean countries (0.7%) compared to women born in the UK (0.5%) is reported by the Office for National Statistics,[326] but these data suggest that the disparity between ethnicities among women with chronic hypertension is much greater. In this cohort, there was greater sensitivity (40% versus 16%) for infants needing neonatal unit admission identified as <3rd birthweight centile using centiles customised for ethnicity (GROW) compared to Intergrowth-21st birthweight centile (without such customisation), and only a small difference in specificity (93% versus 96%). Though ethnicity is not a modifiable factor, these data provide a focus for future research into aetiology and should be considered when investigating modalities of intervention. Also, an awareness of these risk factors should inform antenatal care pathway stratification.

To our knowledge, this is the largest cohort study of women with chronic hypertension in pregnancy examining the risk factors for adverse perinatal outcome in the UK. The data were collated from three tertiary centres, which reduces the risk of confounding found in single centre studies. Robust statistical methodology using regression modelling has allowed for identification and quantification of the impact of maternal factors on subsequent perinatal outcome.

It was not possible to assess severity of chronic hypertension within the cohort. Coding for superimposed pre-eclampsia was not sufficiently reliable and so the additional impact of this diagnosis on adverse perinatal outcome could not be assessed. Additionally, adequately detailed data on blood pressure control, antihypertensive treatment and other maternal co-morbidity were not available. The surrogate outcome of high dependency unit admission was used to assess severity of disease and women of Black ethnicity were significantly more likely to require this level of care after delivery (compared to White women), suggesting a correlation with increased disease severity amongst this group, and supported by a significantly higher proportion of preterm births that were iatrogenic among mothers of Black ethnicity compared to White. This corresponds with the findings of another recent study that found an association between Black ethnicity and iatrogenic preterm delivery.[315] Comparison of temporal changes in care between the national UK data and the cohort was not possible due to restrictions in the availability of NHS data for this timeframe. The only outcome that appeared to improve over time within the cohort was neonatal unit admission. Utilising the national UK data as a comparator in this study was also limited by the large amount of missing data. Future investigation would include collection of all maternity data from the centres included for this time period.

The proportion of Black women in the study was much higher than the national average, although typical of the ethnic mix in large cities in the UK. This may have improved the power for comparison between Black and White women, but is a limitation for comparison with the national pregnancy outcome data. There were smaller numbers of women of Asian ethnic origin compared to other groups and further investigation of ethnic variation in outcome in women of Asian ethnicity is needed. It was also not possible to assess the impact of ethnic sub-groups on risk, for example African ancestry compared to Caribbean.

The risk factors for de novo postnatal hypertension that were identified by Goel and colleagues (2015) in a cohort of 744 women included: raised BMI, Black ethnicity and pre-existing diabetes.[327] A previous UK study published in 1998 included only 213 pregnancies complicated by chronic hypertension and was not powered to compare many of the perinatal outcomes between ethnic groups.[317] The number of adverse perinatal events in this cohort allows for such comparison. The incidence of chronic hypertension in Black women is known to be higher than in White women. There are also well described differences in pathophysiology causing hypertension that are related to ethnicity.[27,328] Variation in socioeconomic circumstances have

previously been linked to these differences,[329] but these cannot account entirely for the differences given that the model presented here included deprivation score as a baseline characteristic and the participants had free point-of-care access to a healthcare system for their antenatal care. However, it was not possible to capture adherence to treatment or engagement in care in this cohort, which may be a factor. Rowe and colleagues found that the odds of late booking after 18 weeks' gestation for antenatal care in England were higher for Black women (odds ratio 5.92; 95% confidence intervals 2.97 to 11.83).[330] There may be cultural reasons or language barriers as to why women do not access or utilise healthcare equally. However, the FASTER trial examined the ethnic variation in perinatal outcomes in women who accessed antenatal care in the first trimester and found that women of Black ethnicity still had an increased risk of perinatal morbidity compared to White women (odds ratio 3.5; 95% confidence intervals 2.5 to 4.9)[331], so this cannot entirely account for the inequality in outcome.

Comparison of customised and non-customised birthweight centiles has been highlighted by recent studies in the general pregnant population.[332,333] The importance of accounting for maternal ethnicity in the calculation of birthweight centiles is unclear. Ethnicity has a strong association with adverse outcome within this population of women with chronic hypertension and birthweight centiles customised for ethnicity have greater sensitivity and comparable specificity in association with an important outcome indicative of adverse perinatal outcome. Classification of fetal and hence neonatal growth restriction has recently been examined by a Delphi consensus outlining criteria for diagnosis of fetal growth restriction.[65] Further investigation into classification of neonatal growth restriction and the importance of including ethnicity within birthweight centile calculation is warranted.[65,334]

Stillbirth, preterm birth, neonatal unit admission and small for gestational age infants are all increased in pregnancy complicated by chronic hypertension. Whilst there have been many advances in caring for premature babies, the long term health implications must not be underestimated and there is growing evidence of the increased risk to the cardiovascular and metabolic health of the growth restricted infant.[335,336] When planning antenatal care pathways for women with chronic hypertension the additional risk factors of ethnicity, maternal age, parity, smoking, and deprivation level on outcome should be considered. Strategies to ensure women of Black and other ethnic minority groups engage with antenatal care and are aware of the increased risks associated with chronic hypertension complicating pregnancy need to be

developed. Additionally, consideration of the other modifiable interventions stratified by ethnicity including thresholds of pre-pregnancy blood pressure control warrants further investigation.

There are marked ethnic disparities in pregnancy outcome in the UK in women with chronic hypertension. Further research is needed to explore the aetiology behind these differences. Variation in the pathophysiology underpinning primary hypertension exists.[337] Outside pregnancy, national recommendations in the UK and the US are that first-line antihypertensive agents are stratified based on ethnicity with Black women receiving calcium-channel blockers rather than angiotensin-converting enzyme inhibitors.[1,77] Consideration of the potential role of first-line antihypertensive agent choice in women of African and Caribbean family origin, as is used outside pregnancy for the treatment of chronic hypertension, is recommended, in order to evaluate whether this strategy might improve maternal and perinatal outcomes. Investigation of the impact of genetics in addition to environmental and cultural variations may improve our understanding of why there is ethnic variation in outcome and how this might be ameliorated.

In conclusion, non-White ethnicity, deprivation, advanced maternal age, primiparity, and smoking status all increase the risk of adverse perinatal outcome in women with chronic hypertension. Ethnicity has the largest impact, with Black women with chronic hypertension at greatest risk. Further research is needed to explore the aetiology underpinning these disparities. An awareness of these differences should inform stratification of antenatal care and treatment pathways.

CHAPTER 5 LABETALOL OR NIFEDIPINE AS ANTIHYPERTENSIVE TREATMENT FOR CHRONIC HYPERTENSION IN PREGNANCY: THE PANDA RANDOMISED CONTROLLED FEASIBILITY TRIAL

5.1 Abstract

Data from randomised controlled trials to guide the choice of antihypertensive agent for pregnancy complicated by chronic hypertension are limited. This study aimed to compare labetalol and nifedipine for control of chronic hypertension in pregnancy, with additional assessment of the impact of ethnicity on efficacy of each treatment. Pregnant women with chronic hypertension (12^{+0}-27^{+6} weeks' gestation) were enrolled at four UK maternity centres between August 2014 and October 2015. Open-label first-line antihypertensive treatment was randomly assigned via an online minimisation protocol with two treatment groups: labetalol (200-1800 mg/day) or nifedipine MR (20-80 mg/day). Biomarkers and pulse wave analyses were measured antenatally. All other antenatal care was standard. Analysis included 112 women (98%) who completed the study (labetalol n=55, nifedipine n=57). Mean monthly recruitment was 2.6 (range 1.2-3.7) women per centre. Interventions were discontinued by seven women (13%) assigned labetalol and five (9%) assigned nifedipine. Maximum blood pressure (BP) post-randomisation was 161/101 mmHg on labetalol versus 163/105 mmHg on nifedipine (mean difference systolic: 1.2 mmHg ((95% confidence interval) -4.9 to 7.2 mmHg), diastolic: 3.3 mmHg (-0.6 to 7.3 mmHg)). Mean BP was 134/84 mmHg on labetalol and 134/85 mmHg on nifedipine (mean difference systolic: 0.3 mmHg (-2.8 to 3.4 mmHg), and diastolic: -1.9 mmHg (-4.1 to 0.3 mmHg)). Nifedipine use was associated with a 7.4 mmHg reduction (-14.4 to -0.4 mmHg) in central aortic pressure, measured by pulse wave analysis. No difference in treatment effect was observed in Black women (n=63), but a mean 4 mmHg reduction (-6.6 to -0.8 mmHg; P=0.015) in brachial diastolic BP was observed with labetalol compared to nifedipine in non-Black women (n=49). Labetalol and nifedipine control mean BP to target in pregnant women with chronic hypertension. Good recruitment was demonstrated and mechanistic treatment effects observed. This study provides support for a larger definitive trial scrutinising the benefits and side effects of first-line antihypertensive treatment in pregnancy complicated by chronic hypertension.

5.2 Introduction

With only three randomised controlled trials (total 101 women)[264,265,275], data to inform prescribing of antihypertensive treatments for chronic hypertension in pregnancy are sparse and subsequently no consensus on the optimal agent(s) exists.[14,16,256,338] The prevalence of chronic hypertension in pregnancy is estimated at 3%,[7] but this figure is set to increase with rising maternal age and the global obesity epidemic.[5,34,39] Given that chronic hypertension is associated with significantly increased adverse maternal and perinatal outcomes compared to the general pregnant population,[8,29,30] defining optimal antihypertensive treatment(s) is warranted.[16]

A Cochrane review examining trials (including over 4000 women) in mild to moderate hypertension in pregnancy (combining chronic and gestational hypertension) concluded that though the incidence of severe hypertension is reduced with antihypertensive treatment, no reduction in the incidence of adverse maternal and perinatal outcomes has been demonstrated.[256] There have been additional concerns that antihypertensive treatment might increase the risk of fetal growth restriction.[129] However, more recent evidence from the Control of Hypertension In Pregnancy Study (CHIPS) concluded that 'tight control' to a diastolic target of 85 mmHg (compared to 'less-tight control' to a diastolic target of 105 mmHg) did not increase the risk of pregnancy loss or high-level neonatal care.[15] This study also demonstrated that the incidence of severe maternal hypertension was significantly increased with 'less-tight' control and that this was associated with an increased risk of serious maternal morbidity in these women (post-hoc analysis).[133] The study highlights the need to determine which antihypertensive agent(s) provides optimal control of chronic hypertension in pregnancy to ameliorate these risks.

Choice of antihypertensive outside pregnancy depends on ethnicity[1,77] and is thought to relate to differences in the pathophysiology causing hypertension in those of differing ethnic backgrounds.[81] Ethnic disparity in maternal and perinatal outcome in the general pregnant population is well described and likely to be multifactorial.[313,314,339,340] No randomised controlled trials have investigated the impact of ethnicity on efficacy of antihypertensive treatment in pregnancy. The aims of the 'Pregnancy And chronic hypertension: NifeDipine versus lAbetalol as antihypertensive treatment' (PANDA) study were three-fold: to assess feasibility of such a randomised controlled trial, to evaluate mechanistic treatment effects, and to examine the impact of ethnicity on efficacy of each treatment.

5.3 Methods

This randomised controlled feasibility trial compared effectiveness of two antihypertensive agents commonly used as first-line treatment[14,16] (labetalol and nifedipine) for the control of chronic hypertension in pregnancy and additionally enrolled pregnant women with chronic hypertension who were unwilling or unable to be randomised to antihypertensive treatment to a parallel observational arm.

Study Design

The main study was an open-label, phase four, feasibility randomised controlled clinical trial (EudraCT Number 2013-003144-23), registered with ISRCTN (DOI 10.1186/ISRCTN40973936, www.isrctn.com); the protocol, and other study literature were approved by the UK Research Ethics Committee (REC number 13/EE/0390). Women of all ethnicities were enrolled by study investigators using written informed consent at four consultant-led National Health Service (NHS) obstetric units in the United Kingdom (Guy's and St Thomas' NHS Foundation Trust, Central Manchester University NHS Foundation Trust, University of Leicester Hospitals NHS Trust and St George's University Hospitals NHS Foundation Trust). The eligibility criteria included: women with a prenatal diagnosis of chronic hypertension or blood pressure (BP) readings ≥140/90 mmHg prior to 20 weeks' gestation requiring antihypertensive treatment, as defined by the International Society for the Study of Hypertension in Pregnancy,[21] gestation between 12^{+0} and 27^{+6} weeks (to allow for second trimester blood pressure nadir), singleton pregnancies, aged over 18 years, and the ability to provide written informed consent. Women were excluded if they had a contraindication or relative contraindication to either antihypertensive agent, such as labetalol in women with asthma. An overview of the study activities are outlined in Figure 5.1.

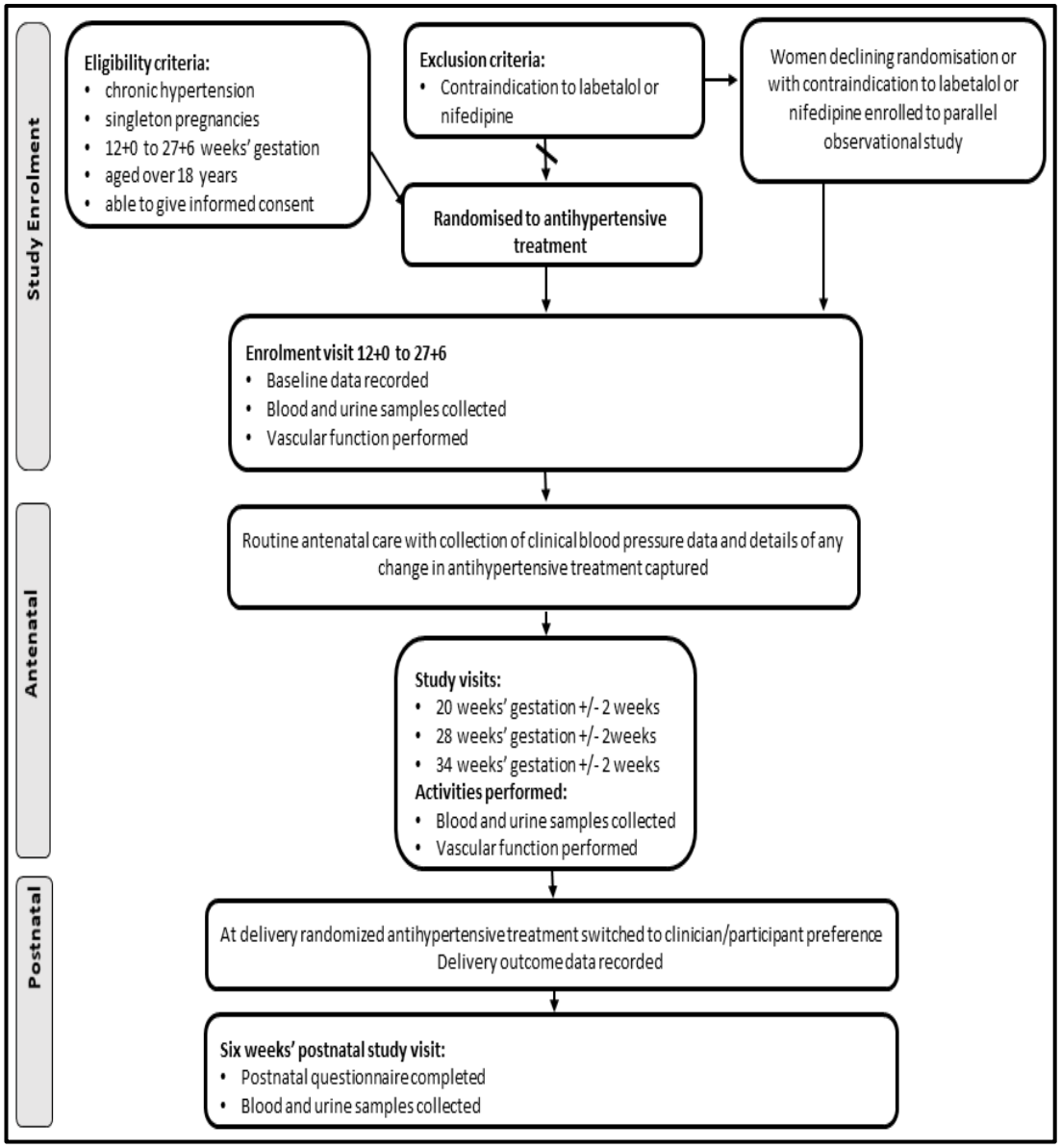


Figure 5.1 Overview of study activities for participants

Although not mandatory for a feasibility study, a pre-trial power calculation was performed to guide enrolment targets and funding requests, and used the highest systolic BP as a continuous outcome with a standard deviation of 7 mmHg (from data analysed in the Vitamins In Pregnancy trial)[341]. The power calculation was based on testing for non-inferiority of nifedipine as compared to labetalol; specifically, a difference of under 4 mmHg. If there was no difference between the two treatments, then complete data on 108 women was required to give 90% power using a one-sided test.[342] A one-sided test is generally considered appropriate for non-inferiority studies. 114 women were recruited to allow for 5% study withdrawal and loss to follow-up. A non-inferiority design was chosen as the study aimed to demonstrate equal effectiveness of the antihypertensive agents under investigation. A Data

Monitoring Committee and Trial Steering Committee were convened at regular intervals during the study to monitor trial conduct, but without interim analysis. The Data Monitoring Committee was provided with reports outlining balance of intervention allocation by each minimisation criteria to ensure even assignment between treatment groups. Stopping guidelines were outlined in the study protocol. Monitoring was conducted by the King's Health Partners Clinical Trials Office at regular intervals at all participating centres during the trial.

Randomisation and Intervention

Women were randomly assigned antihypertensive treatment via a MedSciNet online minimisation protocol with stratification for: gestation at randomisation (divided into four week groups: 12^{+0}-15^{+6}, 16^{+0}-19^{+6}, 20^{+0}-23^{+6} and 24^{+0}-27^{+6}), maternity centre, systolic BP at randomisation (<140 mmHg, 140-149 mmHg and ≥150 mmHg), and ethnicity (Black (determined by self-report of whether the woman had a parent or grandparent who was African or Caribbean) versus non-Black (all other ethnicities)). Minimum divided daily doses of labetalol were 200 mg and maximum 1800 mg and for nifedipine MR 20 mg and maximum 80 mg. Starting doses were decided by the attending clinician. Treatment was open-label as it was considered clinically not feasible to mask allocation to clinicians and women in view of the differing recommended dosing frequency and the need to escalate treatment and add a second agent where needed. Allocated treatment was taken as first-line antihypertensive agent until delivery and replaced any antihypertensive treatment taken at study enrolment (or discontinuation at clinician or woman's request) and women were followed-up until six weeks post-partum wherever feasible. If additional antihypertensive agents were required or women opted to discontinue their assigned intervention, treatment was prescribed at their clinician's preference. Diastolic BP treatment target was 85 mmHg in accordance with recommendations from the outcomes of the Control of Hypertension In Pregnancy Study (CHIPS).[15] Clinical blood pressures were recorded using manual and automatic machines already in use in clinical areas and no restrictions were placed on the positioning of the participants during blood pressure measurement. All other antenatal care was as standard, including concurrent treatment with aspirin 75mg/day as recommended by NICE guidance.[16]

Outcome Measures

Primary outcome measures

The primary process outcome was the number of women enrolled per site per month (calculated at the end of trial as total number of women enrolled per site divided by number of months of enrolment at that site)and the primary clinical outcome was the highest systolic blood pressure between randomisation and delivery (highest of any recorded systolic blood pressure measurement made between gestation at randomisation and gestation at delivery, excluding recordings made on the day of delivery) and in addition the mean systolic blood pressure during each pregnancy between randomisation and delivery will be calculated (using all available systolic blood pressures taken clinically and measured using the trapezium method analysing the area under the curve).

Secondary outcome measures

Secondary clinical outcomes, with effect size calculated, included: proportion of days with BP recordings of systolic BP >=160 mmHg, >=150 mmHg, or diastolic BP <80 mmHg between randomisation and delivery, proportion of women diagnosed with superimposed pre-eclampsia (defined as new-onset proteinuria, a sudden increase in proteinuria if already present in early gestation, and an increase in hypertension)[343], median gestation at delivery, mean birthweight, and proportion of infants admitted to the neonatal care unit in each group. Other secondary clinical outcomes recorded included: additional antihypertensive agent use (oral and parenteral), mode of delivery, estimated blood loss, other adverse maternal outcome (eclampsia, intracranial haemorrhage or infarct, myocardial ischaemia/ infarction, intubation, pulmonary oedema, hepatic dysfunction, acute renal insufficiency, placental abruption, post-partum haemorrhage), condition of the fetus at birth (including Apgar score and umbilical cord gas analysis), customised birthweight centiles, and other adverse neonatal outcomes (respiratory distress syndrome, need for ventilator support, intraventricular haemorrhage, confirmed infection, necrotising enterocolitis, seizures, encephalopathy, and retinopathy of prematurity). Customised birthweight centiles were calculated using the GROW formula with adjustment for maternal height, maternal weight, maternal ethnicity, parity, infant sex, infant birthweight and gestation at birth (version 6.7.5.1 (2014)).[322] Secondary process outcomes included: proportion of women withdrawing from the study, proportion of women able to adhere to the assigned intervention, and proportion and range of adverse events reported in each treatment arm. Health resource use was captured as antenatal outpatient visits (including scans, antenatal clinic and maternity assessment unit visits), antenatal and postnatal

maternal ward nights, maternal intensive care and high dependency unit nights, neonatal intensive care and high dependency care unit nights, neonatal special care and transitional care nights, and neonatal postnatal ward nights. Women were asked to complete a questionnaire regarding their views on trial participation at the six-week follow-up. Planned collection of data from home BP readings was not feasible as few women monitored their BP at home in this cohort. Assessment of adherence through pill count was planned, but not implemented to reduce the time commitment involved in study participation.

Pre-specified mechanistic analyses included: collection of blood and urine samples for biomarker assessment (including placental growth factor (PlGF), syndecan-1, renin, aldosterone, angiotensinogen: creatinine ratio (AGTCR), albumin: creatinine ratio (ACR), and protein: creatinine ratio (PCR) quantification), and pulse wave analyses that were obtained using the Arteriograph® (Tensiomed, Budapest, Hungary) at randomisation, 20 weeks, 28 weeks, 34 weeks' gestation. All pulse wave measurements were performed with participants in the sitting position. The Arteriograph® cuff was then applied to the left arm over the brachial artery for estimation of central aortic pressure (mmHg), pulse wave velocity (m/s) and augmentation index (%) as previously described by Khalil and colleagues (2012).[231] All recordings were made by researchers who had received appropriate training on the use of the Arteriograph®. The results of the pulse wave analyses were not given to the women or their doctors and did not influence the subsequent management of the pregnancies.

Statistical analysis

For the primary analysis, the intention to treat principle was applied; women were analysed in the groups into which they were randomly allocated regardless of allocation received. The statistical software Stata/SE version 14 for Windows was used for all analyses. The number and percentage were calculated for binary and categorical variables. The mean and standard deviation (SD) or the median and interquartile range (IQR) were calculated for continuous variables. Linear regression with robust standard errors (SE) were used for the primary and other continuous outcomes. Adjustment was made for baseline covariates (ethnicity, gestational age at randomisation and centre). For continuous measures, an adjustment was also made for corresponding baseline measurement (systolic BP at randomisation for the primary clinical outcome). For binary outcomes, binary regression with a log link was used to calculate risk ratios (RR). Analysis of the primary clinical outcomes was repeated excluding

women delivering their baby before 24 completed weeks of pregnancy, as women who deliver before viability did not complete the intended course of treatment.

Subgroup analyses assessing the impact of ethnicity on treatment efficacy were performed using linear regression adjusting for baseline co-variates. Results are reported for both groups and an interaction test carried out for any moderation of the treatment effect by the subgroup. A sensitivity analysis was also performed to evaluate the impact of date recruited on the primary outcome, using linear regression with a treatment × time interaction. Explanatory analysis of longitudinal biomarkers (excluding women with Chronic Kidney Disease) and pulse wave measures was conducted using interval regression models on log-transformed data allowing for gestation effects and the baseline measures. This approach made optimal use of all measurements and increased power by combining four techniques: transforming to a Normal distribution, the use of interval regression to include concentrations too small to be measured as censored at the lower limit of detection (rather than discarding them), combining all measurements in a single regression model, and the use of the pre-randomisation measurement as a covariate (a technique also known as ANCOVA). Group means and treatment effects were calculated as geometric means and ratios of geometric means given that log transformations were used. Serious adverse events and adverse events were collated and listed by allocation and grouped by symptom. Treatment effects were calculated as estimated differences in the mean or risk ratios with 95% confidence intervals.

5.4 Results

Between August 2014 and October 2015, 265 women were screened to enter the trial (flow of trial participants is shown in Figure 5.1), of whom 65% met all eligibility criteria. The most common reason for ineligibility was inaccurate information regarding the diagnosis of chronic hypertension captured on booking referral letters or at booking appointments (e.g. previous gestational hypertension). Nine women (3%) were ineligible as they had a concurrent diagnosis of asthma and labetalol was therefore contraindicated. There were no women with a contraindication to nifedipine MR. Of eligible women, 66% agreed to participate. The most common reason given for declining participation was reluctance to change from their current antihypertensive therapy. Recruitment stopped when the enrolment target was reached as per the pre-specified primary process outcome. 114 women with singleton pregnancies and a diagnosis of chronic hypertension were randomised to first-line antihypertensive therapy with either labetalol (n=56) or nifedipine (n=58). The participants not included in the analysis included one woman lost to follow-up as she emigrated during her pregnancy, and one who

withdrew due to time constraints of waiting for dispensing from the clinical trials pharmacy and no further information was available. An additional 23 pregnant women with chronic hypertension, but who were unwilling or unable to be randomised to antihypertensive treatment took part in the observational arm of the study and are included in the analyses of Chapter 6 and 7 (Figure 5.2).

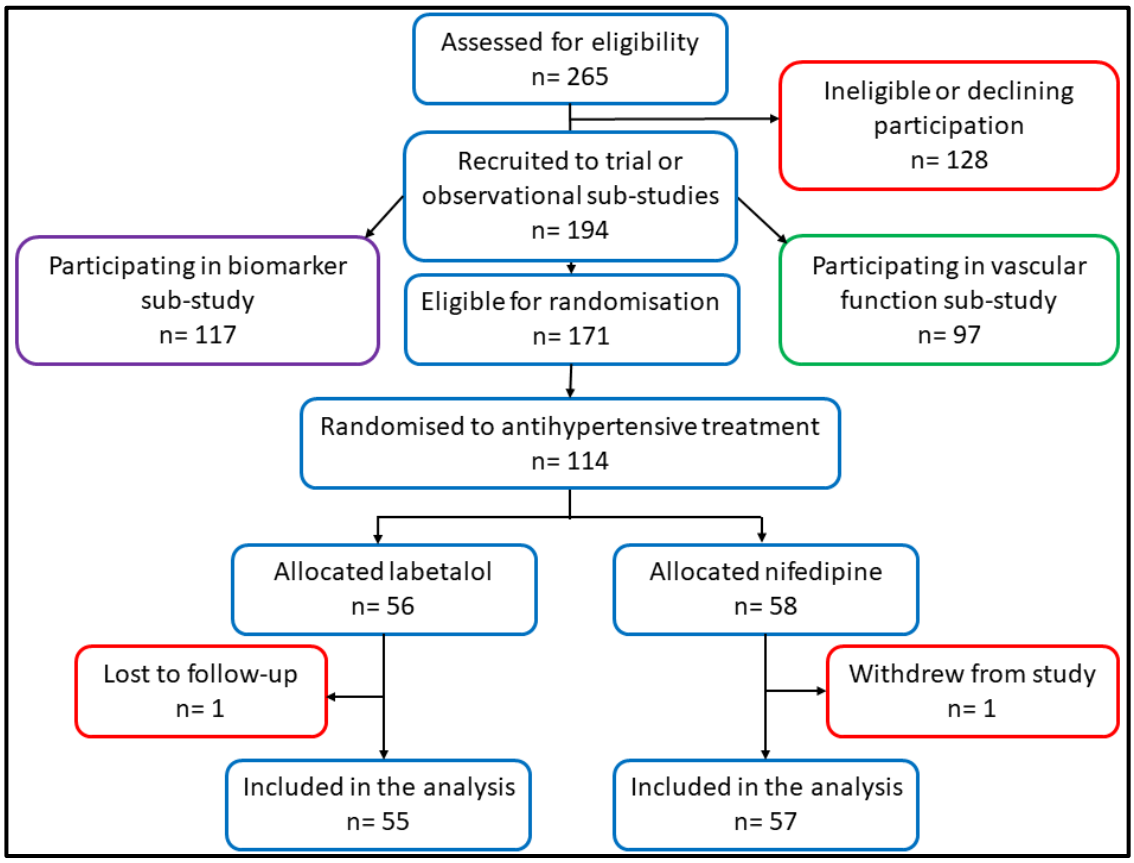


Figure 5.2 Flow diagram of trial and sub-study participants
Blue boxes indicate the flow of trial participants as analysed in Chapter 5, the purple box represents the cohort of women participating in the biomarker sub-study in Chapter 6, the green box represents the cohort of women participating in the vascular function sub-study in Chapter 7, and the red boxes indicate those who were ineligible, declined participation, or lost to follow-up.

Most baseline maternal characteristics at enrolment in each treatment group were similar between treatment groups (Table 5.2), except that time from diagnosis of chronic hypertension to study entry was longer in the labetalol group (54 versus 20 months), and the number of women with renal disease (labetalol n=5 versus nifedipine n=9) and diabetes (labetalol n=5 versus nifedipine n=8) at study entry was higher in the nifedipine group. The results were adjusted allowing for these differences, but this had no significant impact on the outcomes observed (P=0.29).

Table 5.1 Baseline maternal characteristics at enrolment

Characteristic	**Randomised to labetalol n=56**	**Randomised to nifedipine n=58**
Age at enrolment, years median (IQR)	36.0 (32.0-39.1)	35.0 (30.3-38.5)
Gestational age at randomization, weeks median (IQR)	16.6 (13.7-21.3)	16.9 (14.6-21.1)
Ethnicity number (%)		
Black	30 (54%)	32 (55%)
White	17 (30%)	18 (31%)
Asian	6 (11%)	3 (5%)
Other	3 (5%)	5 (9%)
Deprivation quintile* number (%)		
1st	2 (4%)	2 (4%)
2nd	2 (4%)	6 (11%)
3rd	3 (6%)	5 (9%)
4th	14 (27%)	16 (30%)
5th	31 (60%)	25 (46%)
Smoking history number (%)		
Never smoked/ stopped prior to pregnancy	55 (98%)	56 (97%)
Smoking during pregnancy	1 (2%)	1 (2%)
Smoking history unknown	0 (0%)	1 (2%)
Body mass index, kg/m^2 mean (SD) number (%)	31.2 (7.1)	30.5 (4.9)
19-25	17 (30%)	9 (16%)
26-30	13 (23%)	24 (41%)
31-35	9 (16%)	17 (29%)
≥36	17 (30%)	8 (14%)
Previous pregnancies ≥24 weeks' gestation number (%)		
0	14 (25%)	13 (22%)
1	15 (27%)	21 (36%)
2	16 (29%)	14 (24%)
≥3	11 (20%)	10 (17%)
History of pre-eclampsia number (%)	15 (27%)	16 (28%)
Time since diagnosis of chronic hypertension, months median (IQR)	53.5 (8.3-109.5)	20.4 (1.1-75.1)

Type of Chronic Hypertension Number (%)		
Primary	51 (91%)	48 (83%)
Secondary	5 (9%)	10 (17%)
Other medical history number (%)		
Venous thromboembolism	2 (4%)	1 (2%)
Diabetes mellitus (type I or type II)	5 (9%)	8 (14%)
Renal disease	5 (9%)	9 (16%)
Cardiac disease	2 (4%)	0
Systemic lupus erythematous/ Anti-phospholipid syndrome	1 (2%)	1 (2%)
Uterine artery Dopplers number (%)	46 (84%)	45 (79%)
Pulsitility Index Mean (SD)	1.0 (0.4)	1.2 (0.4)
Pulsitility Index >1.4 Number (%)	5 (11%)	11 (24%)
BP at booking, mmHg mean (SD)		
Systolic	136 (125-144)	138 (128-144)
Diastolic	88 (81-92)	86 (80-90)
BP at study entry, mmHg median (IQR)		
Systolic	143 (133-150)	141 (132-151)
Diastolic	92 (85-98)	91 (86-96)
Oral antihypertensive medication taken at study entry number (%)	41 (73%)	38 (66%)

** n=52 in the labetalol group and n=54 in the nifedipine group as unable to link postcodes to lower super output areas and therefore unable to assign deprivation index. SD= standard deviation, IQR= interquartile range*

Feasibility Outcomes

The feasibility of conducting this trial in women with chronic hypertension in pregnancy was confirmed (Table 5.2), with the enrolment target reached over 14 months. Sites with a dedicated antenatal clinic where the women with chronic hypertension were seen found this facilitated identification of eligible women and enrolment to the trial. Recruitment rate was 2.6 women per month (range of 1.2-3.7 per month). Women self-identifying as of Black ethnicity accounted for 56% of those enrolled, confirming feasibility of recruiting women of differing ethnic backgrounds. Geographical variation in the proportion of Black women enrolled was seen reflecting the demographics of the local population of each hospital. The

assigned intervention was discontinued by 12 women due to side effects of the medication; seven (13%) in the labetalol arm and five (9%) in the nifedipine arm.

Table 5.2 Summary of feasibility outcomes

Feasibility outcome	**Total number enrolled n=114**
Women enrolled per centre number (%)	
Guy's and St Thomas' NHS Foundation Trust	56 (49%)
Central Manchester University Hospitals NHS Foundation Trust	33 (29%)
University Hospitals of Leicester NHS Trust	12 (11%)
St George's University Hospitals NHS Foundation Trust	13 (11%)
Enrolment rate per centre (women enrolled per month site recruiting)	
Guy's and St Thomas' NHS Foundation Trust	3.7
Central Manchester University Hospitals NHS Foundation Trust	2.8
University Hospitals of Leicester NHS Trust	1.2
St George's University Hospitals NHS Foundation Trust	1.9
Mean of all centres	2.6
Proportion of those enrolled of Black ethnicity	
Guy's and St Thomas' NHS Foundation Trust	70%
Central Manchester University Hospitals NHS Foundation Trust	46%
University Hospitals of Leicester NHS Trust	17%
St George's University Hospitals NHS Foundation Trust	77%

Clinical Outcomes

Labetalol and nifedipine demonstrated effectiveness at controlling BP to therapeutic target in women with chronic hypertension in pregnancy (mean BP post-randomisation: labetalol 134/84 mmHg versus nifedipine 134/85 mmHg). No difference was observed in highest brachial BP following randomisation to either treatment arm (Table 5.3). A sensitivity analysis excluding those who delivered before 24 weeks' gestation and evaluating the impact of date recruited had no effect on the results. Further analysis of the number of days with brachial BP readings out of target ≥160 mmHg systolic, ≥150 mmHg systolic, and <80 mmHg diastolic demonstrated no difference between treatment groups.

Table 5.3 Effect of treatment on brachial blood pressure

	Randomised to labetalol n=55	Randomised to nifedipine n=57	Adjusted mean difference (95% Confidence Interval)
Maximum BP, mmHg mean (SD)			
Systolic	161 (14.7)	163 (19.2)	1.2 (-4.9 to 7.2)
Diastolic	101 (10.2)	105 (11.7)	3.3 (-0.6 to 7.3)
Mean BP, mmHg mean (SD)			
Systolic	134 (8.5)	134 (9.2)	0.3 (-2.8 to 3.4)
Diastolic	84 (6.6)	85 (5.5)	-1.9 (-4.1 to 0.3)

Results adjusted for systolic BP at randomisation ethnicity, gestational age at randomisation and centre. SD= standard deviation

Secondary maternal and perinatal outcomes (Table 5.4) showed more women on nifedipine developed superimposed pre-eclampsia than those allocated labetalol, but these differences were not significant (RR 1.78; 0.84-3.77). The same number of women in each group were diagnosed with early onset superimposed pre-eclampsia prior to 34 weeks' gestation (n=6 (11%) in each treatment group). The number of women requiring additional oral antihypertensive agents was comparable between groups. There was a greater proportion of women treated with intravenous antihypertensive agents in the nifedipine group (14% versus 4%). The proportions of women requiring induction of labour and caesarean section were comparable. The median gestation at delivery was similar between groups. Adverse maternal outcomes were reported for 6 (11%) women in the labetalol arm compared to 8 (14%) in the nifedipine arm (Table 5.5).

Table 5.4 Secondary maternal and perinatal outcomes

	Randomised to labetalol n=55	**Randomised to nifedipine n=57**	**Adjusted difference in mean/median or RR (95% CI)**
Time between randomisation and delivery, days mean (SD)	134 (39)	127 (44)	
Superimposed pre-eclampsia number (%)	8 (15%)	15 (26%)	1.78 (0.84-3.77)
Superimposed pre-eclampsia <34 weeks number (%)	6 (11%)	6 (11%)	
Additional oral antihypertensive agents number (%)			
0	37 (67%)	36 (63%)	
1	15 (27%)	20 (35%)	
≥2	2 (4%)	1 (2%)	
Additional intravenous antihypertensive agents number (%)	2 (4%)	8 (14%)	
Adverse maternal outcome* number (%)	6 (11%)	8 (14%)	
Mode of delivery number (%)			
Spontaneous vaginal delivery	22 (40%)	21 (37%)	
Assisted vaginal delivery	2 (4%)	4 (7%)	
Elective prelabour LSCS	9 (16%)	13 (23%)	
Emergency prelabour LSCS	14 (26%)	11 (19%)	
Emergency LSCS in labour	8 (15%)	8 (14%)	
Estimated blood loss at delivery, ml mean (SD)	600 (500)	610 (550)	
Gestation at delivery, weeks median (IQR)	38.6 (37.7-39.4)	38.0 (36.4-39.1)	-0.6 (-1.3 to 0.1)
Preterm birth <37 weeks number (%)	12 (22%)	20 (35%)	
Preterm Birth <34 weeks number (%)	10 (18%)	11 (19%)	
Condition of fetus at delivery number (%)			
Livebirth	51 (93%)	52 (91%)	
Miscarriage	1 (2%)	3 (5%)	

Termination of pregnancy	1 (2%)	1 (2%)	
Stillbirth	2 (4%)	1 (2%)	
Neonatal outcomes	**n=51**	**n=52**	
Apgar Score number (%)			
<7 at 1 min	7 (14%)	9 (17%)	
<7 at 5 min	1 (2%)	1 (2%)	
Paired Cord Gases			
Obtained number (%)	24 (47%)	26 (50%)	
Arterial cord pH median (IQR)	7.23 (7.19-7.29)	7.24 (7.18-7.26)	
Birthweight, g mean (SD)	2957 (790)	2732 (883)	-240 (-589 to 109)
Customised birthweight centile mean (SD)	33.4 (31.2)	27.7 (26.3)	
Birthweight <10th customised centile number (%)	16 (31%)	17 (33%)	
Birthweight <3rd customised centile number (%)	6 (12%)	10 (19%)	
Admitted to neonatal unit number (%)	11 (22%)	15 (29%)	1.3 (0.7-2.5)
Adverse perinatal outcome* number (%)	11 (22%)	17 (33%)	

**Details of adverse maternal and perinatal outcomes provided in Table 5.5 and Table 5.6. Results adjusted for ethnicity, gestational age at randomisation and centre. Risk ratios only calculated for pre-specified secondary outcomes.*
SD= standard deviation, IQR= interquartile range

Table 5.5 Details of adverse maternal outcomes

	Randomised to labetalol n=55	Randomised to nifedipine n=57
Any maternal complication	6 (11%)	8 (14%)
Maternal death	0	0
Central Nervous System		
Eclampsia	0	0
Glasgow coma score <13	0	0
Intracranial haemorrhage or infarct	0	0
Transient ischaemic attack	0	0
Cortical blindness or retinal detachment	0	0
Posterior reversible encephalopathy	0	0
Cardiorespiratory		
Positive inotropic support required	0	0
Myocardial ischaemia or infarction	0	0
Oxygen saturations <90% >2 hours (pre-eclampsia)	0	0
≥50% Oxygen therapy required for >1 h	0	0
Intubation (other than for caesarean section)	0	0
Pulmonary oedema	0	0
Haematological		
Transfusion of any blood product	2 (4%)	5 (9%)
Platelet count <50×10^9 per L, with no transfusion	1 (2%)	0
Hepatic		
Dysfunction	0	0
Haematoma or rupture	0	0
Renal		
Acute renal insufficiency (creatinine >150 µmol/L; no pre-existing renal disease	1 (2%)	0
Acute renal failure (creatinine >200 µmol/L; pre-existing renal disease	1 (2%)	2 (4%)
Dialysis	0	0
Obstetric		
Placental abruption	0	1 (2%)
HELLP syndrome	1 (2%)	0
Postpartum haemorrhage, >1.5L	4 (7%)	4 (7%)

Six women delivered their baby before 24 weeks and three women had a stillbirth after 24 weeks' gestation. Four had late miscarriages (one in the labetalol group and three in the nifedipine group). Two women (one in each treatment group) underwent second trimester termination of pregnancy after enrolling in the study (one for abnormal amniocentesis result post-randomisation and one for severe early onset growth restriction). There were two stillbirths in the labetalol group (both with severe early onset growth restriction) and one in the nifedipine group (trisomy 13 diagnosed on amniocentesis after study enrolment). There was no significant difference in mean birthweight: 2960 g in the labetalol arm versus 2730 g in the nifedipine arm (adjusted mean difference -240 g; -590, 110 g). There was a high proportion of babies born below the 10th and 3rd birthweight centile in each treatment group. Neonatal unit admission was slightly lower in the labetalol group compared to the nifedipine group (22% versus 29%). Adverse neonatal outcomes were reported for 11 (22%) infants in the labetalol arm and 17 (33%) infants in the nifedipine arm (Table 5.6).

Table 5.6 Details of adverse neonatal outcomes

	Randomised to labetalol n=51	**Randomised to nifedipine n=52**
Any neonatal complication	11 (22%)	17 (33%)
Neonatal Death	0	0
Infant death >28 days post delivery	0	1 (2%)
Central nervous system		
Interventricular Haemorrhage	0	0
Seizures	0	0
Encephalopathy	0	0
Retinopathy of prematurity	0	0
Respiratory		
Respiratory Distress Syndrome	7 (14%)	11 (21%)
Need for additional respiratory support	6 (12%)	12 (23%)
Gastrointestinal		
Necrotising enterocolitis	3 (6%)	2 (4%)
Hypoglycaemia	6 (12%)	8 (15%)
Sepsis	1 (2%)	5 (10%)
Congenital anomalies*	1 (2%)	4 (8%)
Chromosomal abnormalities*	0	1 (2%)

Neonatal outcome data is only presented for the livebirths.

***Congenital anomalies by treatment group included; labetalol: one infant with hypospadias; nifedipine: one infant with jejunal atresia and a deletion on the short arm of chromosome 16, one infant with trachea-oesophageal fistula, and one infant with tetralogy of fallot. All of these women were randomised after 16 weeks' gestation.*

Maternal and neonatal health resource use was similar between treatment groups (Table 5.7).

Table 5.7 Health resource use category by randomised treatment group (mean and standard deviation)

Health resource	Randomised to labetalol n=55	Randomised to nifedipine n=57
Number of antenatal clinics, antenatal day unit visits and ultrasound visits in pregnancy	19 (8)	20 (8)
Number of maternal antenatal and postnatal ward nights	4 (3)	7 (7)
Number of maternal intensive care unit and/or high dependency unit nights	0.4 (1.1)	0.9 (1.9)
Number of neonatal intensive care unit and/or high dependency care nights	2 (10)	6 (23)
Number of neonatal special care and/or transitional care nights	2 (6)	3 (12)
Number of neonatal postnatal ward nights	2 (2)	2 (2)

A pre-specified exploratory subgroup analysis of the impact of ethnicity on efficacy of each treatment did not show any significant difference in mean systolic or diastolic brachial BP in Black women (systolic 0.5 mmHg; -4 to 5 mmHg; diastolic 0.1 mmHg; -3 to 3 mmHg). No difference in mean systolic BP was seen between treatment groups in the non-Black women (-0.4 mmHg; -4 to 3 mmHg), but a 4 mmHg (-6.6 to -0.8 mmHg; P=0.015) reduction in mean diastolic BP was seen in the labetalol arm in non-Black women.

Mechanistic Outcomes

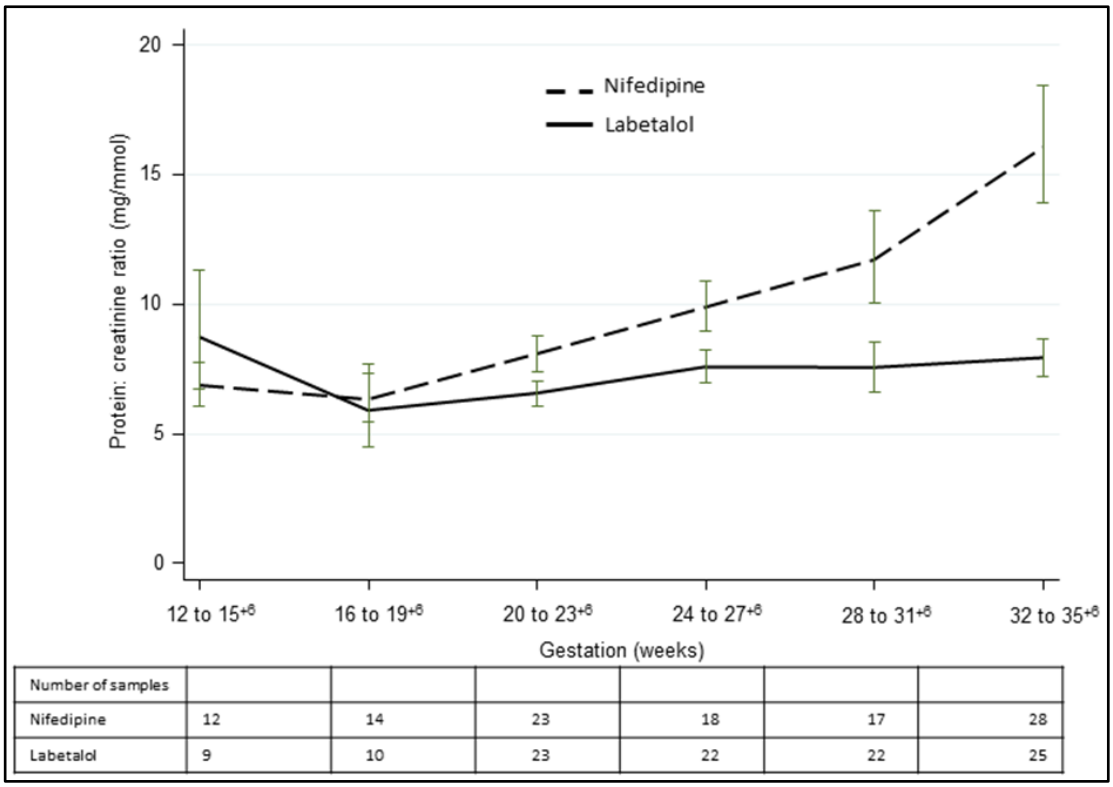
Pulse wave analysis was performed in a subgroup of 83 women at three centres (nifedipine n=43, labetalol n=40). There was a mean 7.4 mmHg decrease (-0.4 to -14.4 mmHg) in central aortic pressure between randomisation and delivery in those assigned nifedipine compared to labetalol. Augmentation index was 8.2% lower (-3.0 to -13.3%) in those assigned nifedipine compared to labetalol, though a sensitivity analysis examining the impact of centre on this finding demonstrated significant variation in this parameter by centre. There was no significant difference in pulse wave velocity between treatment groups (Table 5.8).

Table 5.8 Effect of treatment on pulse wave analysis measures across gestation post-randomisation

Parameter	Randomised to labetalol n=42 mean (SD)	Randomised to nifedipine n=45 mean (SD)	Adjusted mean difference post-randomisation (95% CI)	P value
Central aortic pressure, mmHg	132 (20.2)	126 (12.9)	-7 (-0.4 to -14.4)	0.04
Augmentation index, %	21 (14.9)	13 (11.7)	-8.2 (-3.0 to -13.3)	0.002
Pulse wave velocity, m/s	8.8 (1.7)	8.7 (1.5)	-0.1 (-0.4 to 0.7)	0.62

Pulse wave analyses were only assessed at three sites, which accounts for the reduction in the number of participants presented for this analysis. Results adjusted for baseline measures, gestation and repeat readings from the same women.
SD=standard deviation

Analysis of gestational change in urinary PCR by treatment group included samples from 73 women (collected at three centres) without chronic kidney disease (nifedipine n=35, labetalol n=38). The PCR increased by 44% (21 to 71%) across gestation post-randomisation in women assigned nifedipine compared to women prescribed labetalol (Figure 5.3). The mean PCR post-randomisation was 11.5 mg/mmol (SD 1.9) in the nifedipine group compared to 7.5 mg/mmol (SD 1.8) in the labetalol group. The analysis was repeated excluding the women who developed superimposed pre-eclampsia (labetalol n=35 versus nifedipine n=27) with minimal effect on the results; PCR increased by 43% (18 to 74%) and the mean PCR post-randomisation was 11.5 mg/mmol (SD 1.9) in the nifedipine group compared to 7.4 mg/mmol (SD 1.9) in the labetalol group. Urinary ACR analysis demonstrated a similar increase in those randomised to nifedipine compared to labetalol, but no other treatment effects were observed on the biomarkers tested (PlGF, syndecan-1, renin, aldosterone and AGTCR).



Number of samples						
Nifedipine	12	14	23	18	17	28
Labetalol	9	10	23	22	22	25

Figure 5.3 Treatment effects on urinary protein: creatinine ratio across gestation post-randomisation

Number of participants sampled at each time point is detailed in the table below the graph and the standard error bars are included at each time point.

Adverse Events and Acceptability

There were four Serious Adverse Events reported, all for unplanned hospital admissions not related to the pregnancy: one was in the labetalol arm (admission for epistaxis) and three in the nifedipine arm (one case of gastroenteritis, one case of deep vein thrombosis and one case of influenza). None were deemed to be related to the assigned intervention. The adverse events reported are presented in Table 5.9. In the labetalol group, 21 (38%) women reported an adverse event compared to 15 (26%) in the nifedipine group. The postnatal questionnaire was answered by 34% of the women who completed the study. When asked if they would take the same treatment again in another pregnancy, 72% of the women taking labetalol said they 'definitely would' compared to 90% of those assigned nifedipine, and 11% of those assigned labetalol said they 'probably would not' take the treatment again compared to 5% of those assigned nifedipine.

Table 5.9 Summary of adverse events reported in each treatment arm

Adverse events, n (%)	Randomised to labetalol n=55	Randomised to nifedipine n=57
Total	21 (38%)	15 (26%)
Headache	10 (18%)	11 (19%)
Dizziness	5 (9%)	2 (4%)
Lethargy	2 (4%)	0
Epistaxis	1 (2%)	1 (2%)
Scalp tingling	2 (4%)	0
Shortness of breath	5 (9%)	1 (2%)
Abdominal pain/nausea	2 (4%)	2 (4%)
Peripheral oedema	2 (4%)	1 (2%)
Chest pain	1 (2%)	0
Hot flushes	1 (2%)	1 (2%)
Eye spasm	1 (2%)	0
Nasal congestion	1 (2%)	0
Nipple pain	1 (2%)	0

5.5 Discussion

To our knowledge this is the first randomised controlled feasibility trial comparing labetalol and nifedipine for control of chronic hypertension in pregnancy. These are two of the most commonly used agents in many countries for treatment of hypertensive disorders of pregnancy. This study confirms the high prevalence of adverse maternal and perinatal outcomes in women with chronic hypertension in pregnancy; 21% developed superimposed pre-eclampsia, 8% experienced fetal loss, 32% of infants were small for gestational age (birthweight <10th centile), 16% had a birthweight <3rd centile, and 25% required neonatal unit admission, similar to that reported in a recent systematic review.[8] Recruitment to randomised controlled trials of medication in pregnancy is challenging in view of the real and perceived risk of fetal harm. We confirmed the feasibility of conducting a randomised controlled trial investigating effectiveness of first-line antihypertensive agents for the treatment of chronic hypertension in pregnancy Additionally, this feasibility study has produced data allowing exploration of the important characteristics contributing to adequate BP control in such pregnancies. Demonstrating feasibility is important given the costly nature of large multicentre studies and need for suitable pragmatic designs to ensure definitive studies will fully answer the research questions posed.[344] Of the women meeting all eligibility criteria to enter the study, two-thirds consented to participation and 98% completed the study. Ethnic diversity in recruitment was also demonstrated, enabling investigation of variation in treatment efficacy.

This study demonstrates that labetalol and nifedipine can be used to achieve a mean systolic and diastolic BP within treatment target over gestation in pregnant women with chronic hypertension. The maximum and mean BP post-randomisation were comparable between treatment groups; this is clinically important because of the paucity of data available to guide antihypertensive treatment prescribing for chronic hypertension in pregnancy.[14,16,256] Given the potential contraindications (such as labetalol in women with asthma) and the possible side effect profiles of these drugs, evidence that they have similar ability to control hypertension to treatment target is of benefit. The study was not powered to assess variation in the secondary maternal and perinatal outcomes, but further larger trials should evaluate differences in incidence of superimposed pre-eclampsia, preterm delivery and small for gestational age infants. Variation in treatment effect by ethnicity was also noted, with labetalol having a greater effect on reducing diastolic BP in non-Black women, as previously demonstrated with beta-blocker use outside pregnancy.[80] The clinical significance of this difference needs to be established.

Nifedipine use was associated with reduced central aortic pressure and augmentation index. No treatment effect was observed on pulse wave velocity analyses; this is consistent with the findings of the ACCT trial (2005) that augmentation index is a more sensitive marker of arterial stiffening and cardiovascular risk in younger individuals, with pulse wave velocity demonstrating greater association with increased cardiovascular risk in older individuals.[345] Calcium channel blockers (versus beta-blockers) have been demonstrated to lower central aortic pressure in the CAFÉ study (non-pregnant hypertensive population).[244] The exact mechanism behind these haemodynamic differences is not clear, but this finding in combination with the ASCOT trial results (of which 'CAFÉ' was a subgroup analysis) suggested a greater decrease in long term cardiovascular risk with calcium channel blockers as first-line antihypertensive agent compared to beta-blockers, perhaps mediated through this reduction in central aortic pressure.[245] National guidance no longer recommends beta-blockers as first-line antihypertensive treatment outside pregnancy; calcium channel blockers are recommended as first-line antihypertensive treatment in Black women and angiotensin converting enzyme inhibitors (avoided in pregnancy due to fetal risks) are recommended for women under 55 years of age of other ethnic backgrounds.[1,77] African and Caribbean women are at increased risk of chronic hypertension and its associated cardiovascular morbidity, from a younger age than women of other ethnic origins.[328] There is evidence that maternal and perinatal outcomes vary by ethnic background.[313,314,339,340] The implications of the first-line

treatment recommendations outside pregnancy on the selection of antihypertensive agents in pregnancy needs to be investigated further.

Increased proteinuria across gestation with nifedipine use (compared to labetalol) was demonstrated even when those who developed superimposed pre-eclampsia and with pre-existing renal disease were excluded from the analysis. Proteinuria is known to increase during gestation in normotensive pregnancy due to increased glomerular filtration.[223] In this cohort the mean PCR increased post study enrolment by 2.4 mg/mmol. It is not clear if the difference in proteinuria between treatment groups is a beneficial effect of labetalol or a side effect of nifedipine on renal function, and the clinical significance is unclear given the concentrations fall within the normal range. It seems probable that this is a side effect of nifedipine given similar findings in a Cochrane systematic review of an increase in proteinuria/pre-eclampsia in women with mild to moderate hypertension in pregnancy randomised to calcium channel blockers versus none (four studies, 725 women; RR 1.40 (1.06-1.86).[256] Studies in non-pregnant individuals with hypertension and chronic kidney disease suggest that dihydropyridine calcium channel blockers (including nifedipine) are less effective at reducing proteinuria and therefore offer less renal protection than other antihypertensive agents.[346] Investigation into the potential pathophysiology behind these differences has suggested that glomerular hypertension may be caused by dihydropyridine calcium channel blockers that dilate the afferent but not the efferent renal arterioles.[347] The variation in mechanism of action of antihypertensive agents in pregnancy needs to be explored further given that crossing a threshold of proteinuria is utilised in the diagnosis of pre-eclampsia;[348] however the benefits of hypertensive control may outweigh a small increase in proteinuria.

The main strengths of this study include enrolment at four centres located around the UK reducing the risk of clinical practice bias. The study was designed and conducted as a randomised controlled feasibility trial in line with CONSORT guidance.[349] A computer-generated minimisation protocol was used to ensure balance within groups of maternal baseline characteristics. This reduced the risk of imbalance of baseline characteristics within treatment arms affecting the outcomes of the study. The study enrolled women with primary and secondary hypertension, which increases generalisability of the results; however, this introduced potential bias as reflected in the imbalance of women with chronic kidney disease and diabetes between treatment groups.

Whilst this study has confirmed feasibility a larger definitive study is required to assess further the effectiveness of labetalol and nifedipine for control of BP in pregnancy complicated by chronic hypertension. The power calculation utilised an estimated standard deviation in the primary outcome of 7 mmHg, but the standard deviation of the highest systolic blood pressure demonstrated in this study was much greater at 14.7 to 19.2 mmHg. This information can be utilised in the power calculation for the definitive study. The study was not powered to answer the additional question of ethnic variation in effectiveness of first-line antihypertensive agents in pregnancy, but demonstrated the feasibility of recruiting women of all ethnic groups. This was a non-inferiority study, which increased the number of participants required to answer the primary outcome. Consideration should be given to a superiority design for the definitive study, but the findings of this feasibility study suggest that labetalol and nifedipine are comparable for treatment of chronic hypertension in all pregnant women. However, a superiority design should be chosen in a study examining the efficacy of calcium-channel blockers compared to labetalol in women of Black ethnicity with chronic hypertension in pregnancy, given that calcium-channel blockers are recommended as first-line antihypertensive treatment in those of African/Caribbean family origin outside pregnancy.[1]

The study was open-label subjecting the results to potential performance bias.[259] It was considered clinically not feasible to mask allocation to clinicians and women in view of the differing recommended dosing frequency and need to escalate treatment and add a second agent where needed. It was not possible to fully assess clinician adherence to the target blood pressure and treatment regime in this multicentre pragmatic trial and future studies assessing efficacy of individual agents might elucidate further information regarding variation in adherence to such protocols. In this study methyldopa was not included; however recent evidence (though not from a randomised head-to-head comparison) suggested that this agent may be associated with benefit in maternal and perinatal outcome compared to labetalol, and it should be considered for comparison in a definitive trial.[350]

Evidence from the CHIPS trial[15] demonstrates maternal benefit of 'tight control' of BP utilising antihypertensive agents in reducing the incidence of severe hypertension without an increase in adverse perinatal outcomes.[133] This is the largest head-to-head trial in pregnant women with chronic hypertension assessing effectiveness of antihypertensive agents in controlling BP. There are three previous head-to-head studies including 101 women in total that have compared the incidence of severe hypertension between randomised treatment groups (RR

1.1; 0.71-1.81).[264,265,275] Randomised controlled trials comparing antihypertensive treatment of chronic hypertension in pregnancy are limited and most were conducted at least 20 years ago.[302] The antihypertensive treatments compared in this trial are first-line agents maximising the utility of the results in every day practice.[16]

Women with chronic hypertension are at increased risk of cardiovascular morbidity and mortality compared to normotensive women and those with the transient condition of gestational hypertension.[306] A recent trial comparing management strategies for chronic hypertension outside pregnancy (the SPRINT study) stopped recruitment early due to the significant 25% reduction seen in a composite cardiovascular outcome (stroke, myocardial infarction and cardiac failure) with tighter control of systolic hypertension to a target of 120 mmHg rather than the standard treatment target of 140 mmHg; however this was coupled with a significant increase in hypotension, syncope and acute kidney injury.[305] In pregnancy, reducing the incidence of severe hypertension and maintaining tighter BP control might have short and long term maternal health benefits and prevent adverse pregnancy outcomes associated with unnecessary obstetric intervention and acceleration of cardiovascular risk.

Future research should further explore the mechanistic actions of each drug to establish the effectiveness of antihypertensive agents in the chronic hypertensive pregnant population and assess the utilisation of differences in treatment effect on individuals. A definitive trial will need to address potential treatment effects on other maternal and perinatal outcomes such as superimposed pre-eclampsia and fetal growth restriction. The impact of antenatal management strategies in women with chronic hypertension on long term health of the mother and her child should also be considered.

In conclusion, labetalol and nifedipine control mean systolic and diastolic BP to treatment target in pregnant women with chronic hypertension. Good recruitment was demonstrated and mechanistic treatment effects observed. This study provides support for a larger definitive trial scrutinising the benefits and side effects of first-line antihypertensive treatment in pregnancy complicated by chronic hypertension.

CHAPTER 6 CHRONIC HYPERTENSION IN PREGNANCY: THE IMPACT OF ETHNICITY AND SUPERIMPOSED PRE-ECLAMPSIA ON PLACENTAL, ENDOTHELIAL AND RENAL BIOMARKERS

6.1 Abstract

Black ethnicity is associated with worse pregnancy outcomes in women with chronic hypertension. Pre-existing endothelial and renal dysfunction, and poor placentation may contribute but pathophysiological mechanisms underpinning increased risk are poorly understood. This cohort study aimed to investigate the relationship between ethnicity and longitudinal changes in markers of endothelial, renal and placental dysfunction in women with chronic hypertension. In women with chronic hypertension and singleton pregnancies, plasma concentrations of placental growth factor (PlGF), syndecan-1, renin, aldosterone, and urinary angiotensinogen: creatinine ratio (AGTCR), protein: creatinine ratio (PCR) and albumin: creatinine ratio (ACR) were quantified during pregnancy and postpartum. Comparisons of longitudinal biomarker concentrations were made using log-transformation and random effects logistic regression allowing for gestation. Logged estimates with 95% confidence intervals of the geometric means and their ratios to the reference group in each analysis were calculated. Of 117 women, superimposed pre-eclampsia was diagnosed in 21% (n=25); 54% (n=63) of the cohort self-identified as of Black ethnicity. Black women had 43% lower plasma renin (95% confidence interval -58% to -23%) and 41% lower plasma aldosterone (95%CI -45% to -15%) concentrations over gestation. PlGF concentrations were 67% lower (95% CI -79% to -48%), and AGTCR, PCR and ACR were higher over gestation, in women with subsequent superimposed pre-eclampsia (compared to those without superimposed pre-eclampsia). Changes in placental (PlGF) and renal (AGTCR/PCR/ACR) biomarkers predated the development of superimposed pre-eclampsia. Ethnic variation in the renin-angiotensin-aldosterone system exists in women with chronic hypertension in pregnancy and may indicate how treatment can be optimised to improve pregnancy outcomes.

6.2 Introduction

Chronic hypertension is estimated to affect 3% of pregnancies[7,30] and is associated with adverse maternal and perinatal outcome.[8,29] A recent systematic review by Bramham and colleagues (2014) reported a relative risk of superimposed pre-eclampsia of 7.7 (95% confidence interval 5.7 to 10.1) compared to the risk of pre-eclampsia in the general pregnant population.[8] Adverse perinatal outcomes such as stillbirth, fetal growth restriction and prematurity are also more common in women with chronic hypertension and occur independently from a diagnosis of superimposed pre-eclampsia.[43,45,54] Women of Black

ethnicity, compared to women of White ethnicity with chronic hypertension, have an increased risk of superimposed pre-eclampsia,[45] which may be contributory, but greater understanding of the interplay of known biomarkers and ethnicity in women with chronic hypertension may provide insight into pathophysiological mechanisms.

Pre-eclampsia is characterized by placental and maternal vascular dysfunction.[351] Placental growth factor (PlGF) and syndecan-1 are placental and endothelial biomarkers that have previously been shown to decrease in concentration in the maternal circulation prior to the onset of the clinical signs of pre-eclampsia.[199,201,207] A recent study by Chappell and colleagues (2013) has demonstrated that low PlGF, in women presenting before 35 weeks' gestation with suspected preeclampsia, has high sensitivity and negative predictive value for preeclampsia within 14 days.[203] Diagnosing superimposed pre-eclampsia in women with chronic hypertension is challenging because gestational progression of hypertension may occur in response to the physiological changes in pregnancy, without the sequelae of pre-eclampsia. Variation in these biomarkers over gestation in women with chronic hypertension requires further exploration.

The kidney is of critical importance in blood pressure regulation primarily via salt and water homeostasis. A key mechanism underpinning this homeostatic function is the role of the kidney in the systemic renin-angiotensin-aldosterone system (RAAS). Increased glomerular filtration and upregulation of the circulating RAAS are amongst the physiological changes that characterise normotensive pregnancy.[352,353] Changes in the RAAS and other renal biomarkers (protein: creatinine ratio (PCR) and albumin: creatinine ratio (ACR)) have been demonstrated in pre-eclampsia;[225,354] however there are limited data from longitudinal cohorts examining these biomarkers in pregnant women with chronic hypertension.[109] The impact of ethnicity on these biomarkers in pregnancy also requires exploration. Black women are more likely to have low renin hypertension[337] and ethnic differences in RAAS function in pregnancy may partly explain disparity observed in clinical outcome.[314,315]

This study aimed to investigate the longitudinal variation in endothelial and renal biomarkers in women with chronic hypertension in pregnancy, and the impact of subsequent superimposed pre-eclampsia and ethnicity on these biomarkers.

6.3 Methods

This was a nested cohort study of women with chronic hypertension who participated in the 'Pregnancy And chronic hypertension: NifeDipine versus lAbetalol as antihypertensive treatment' trial between 2014 and 2016. The study was registered with ISRCTN (DOI 10.1186/ISRCTN40973936, www.isrctn.com) and approved by the UK Research Ethics Committee (REC number 13/EE/0390). The study was reported in line with STROBE guidance for observational studies.[325]

Study Design

Women were enrolled at three consultant-led National Health Service (NHS) obstetric units in the United Kingdom (Guy's and St Thomas' NHS Foundation Trust, Central Manchester University NHS Foundation Trust, and University of Leicester Hospitals NHS Trust). The eligibility criteria included: women with a prenatal diagnosis of chronic hypertension or blood pressure readings ≥140/90 mmHg prior to 20 weeks' gestation requiring antihypertensive treatment, (as defined by the International Society for the Study of Hypertension in Pregnancy classification of hypertensive disorders of pregnancy,[21]) between 12 and 27.9 weeks' gestation, singleton pregnancies, aged over 18 years, and the ability to provide informed consent. No formal power calculation was performed, but all women participating in the main trial at the sites afore mentioned, were asked to participate in the sub-study. Participants were asked to provide longitudinal samples of blood and urine at study entry and at follow-up antenatal visits across gestation and at six weeks postpartum. Baseline demographic and antenatal booking data were collected at enrolment. Ethnicity (Black versus non-Black) was determined by self-report of a parent or grandparent who was African/Caribbean (Black ethnicity) or not (non-Black ethnicity). Blood pressure readings taken at all subsequent antenatal visits and daily during hospital admissions (highest of that day) were recorded in addition to other maternal and perinatal outcome data (superimposed pre-eclampsia, mode of delivery, gestation at delivery, pregnancy loss, birthweight, birthweight centile and neonatal unit admission). Superimposed pre-eclampsia was defined as new-onset proteinuria, a sudden increase in proteinuria if already present in early gestation, and an increase in hypertension, as defined by the American College of Obstetrics and Gynaecology.[343] Customised birthweight centiles were calculated using the GROW formula with adjustment for maternal height, maternal weight, maternal ethnicity, parity, infant sex, infant birthweight and gestation at birth (version 6.7.5.1 (2014)).[322] Birthweight below the 3rd centile represents fetal growth restriction.[65] Women with PCR >30 mg/mmol at study entry (likely indicative of chronic kidney disease) were excluded from the analysis of urinary biomarkers.

Analysis of Samples

Venous blood and midstream urine samples were placed on ice immediately after collection, spun at 1400xg for 10 minutes and stored at -80˚C within four hours. The following tests were conducted without knowledge of clinical outcomes.

Placental and endothelial biomarkers: Plasma PlGF and plasma syndecan-1 concentrations were measured on all antenatal samples. PlGF was quantified using the Triage PlGF Test (Alere, San Diego, USA) according to the manufacturer's instructions. Syndecan-1 concentrations were measured using a solid phase sandwich ELISA kit for quantification of human syndecan-1 (Abnova, Taipei City, Taiwan), in accordance with manufacturer's instructions.

Renal biomarkers: Plasma renin and aldosterone concentration, and urinary AGTCR, PCR, and ACR were quantified for all samples (antenatal and postnatal). Plasma renin and aldosterone were measured using Diasorin Liaison direct renin and aldosterone reagents respectively (Diasorin, Wokingham, UK), run on the Liaison chemiluminescence analyser.

Urinary angiotensinogen concentrations were determined using a solid phase sandwich ELISA kit (Immuno-Biological Laboratories, Gunma, Japan) according to manufacturer's instructions.[355] The urinary angiotensinogen concentrations were then normalised to urinary creatinine to provide AGTCR. Urinary creatinine, protein and albumin reagents were supplied by Siemens Healthcare Diagnostics Ltd (Camberley, UK). Urinary creatinine reacted with picric acid under alkaline conditions to form a red Janovsky complex (the Jaffé reaction). The initial rate of absorbance change was measured at a wavelength of 505 nm and compared to that of a known calibrant. This was directly proportional to the concentration of creatinine in the sample. A blank reaction rate was performed using reagent 1 (sodium hydroxide, before picrate addition) to minimise interference from bilirubin. Urinary protein forms a blue coloured complex with pyrogallol red, under acid conditions and in the presence of molybdate ions. The absorbance of this complex was measured at 596 nm, and related to that of a previous calibration assay. Urine albumin was measured using a polyethylglycol enhanced immunoturbidimetric method. The sample was diluted and then reacted with antiserum to form a precipitate that was measured turbidimetrically at 340nm. Urine albumin was measured on the Siemens Advia 2400 analyser.

Statistical Analysis

The statistical software Stata version 14 (StataCorp, College Station, Texas) and GraphPad Prism 7 (Graph Pad Software, San Diego, California) were used for all analyses. The

investigation was divided into two parts. Analysis A compared baseline characteristics, clinical outcomes and endothelial and renal biomarkers between women with chronic hypertension who developed superimposed pre-eclampsia and women with chronic hypertension who did not develop superimposed pre-eclampsia. Analysis B compared baseline characteristics, clinical outcomes and endothelial and renal biomarkers between women with chronic hypertension self-identifying as of Black ethnicity with women with chronic hypertension self-identifying as of non-Black ethnicity. An additional analysis examined the relationship between PlGF and birthweight centile. Baseline characteristics and clinical outcomes were compared between subgroups in analyses A and B using t-tests or Mann-Whitney test for continuous variables depending on the distributions and Fisher's exact test for categorical variables. Mean post-enrolment systolic and diastolic blood pressure were calculated using the trapezium method of analysing the area under the curve for each woman. Variation in longitudinal endothelial and renal biomarkers for analyses A and B was assessed using random effects GLS regression with robust standard errors[356] on log-transformed data allowing for gestation effects. Logged estimates with 95% confidence intervals of the geometric means and of their ratios to the reference group in each analysis were calculated. Standard mathematic methods converted these to percentage differences between groups: percent difference = (exp[parameter]– 1) x 100%. An interaction test examining the correlation between ethnicity, diagnosis of superimposed pre-eclampsia and gestation was performed using a random-effects regression model, wherever significant ethnic differences in biomarker concentration were demonstrated.

6.4 Results

The cohort recruited to the study included 121 women with singleton pregnancies and chronic hypertension (Figure 6.1). Longitudinal samples (332 in total) were obtained in 117 (97%) women; outcome data were unavailable for four (3.3%) women (two women lost to follow-up and two withdrew from the study). For analysis A, the cohort was divided into women diagnosed with superimposed pre-eclampsia and compared with women who were not diagnosed with superimposed pre-eclampsia (n=25 versus n=92) and for analysis B, the cohort was divided into women self-identifying as of Black ethnicity versus women self-identifying as of non-Black ethnicity (n=63 versus n=54).

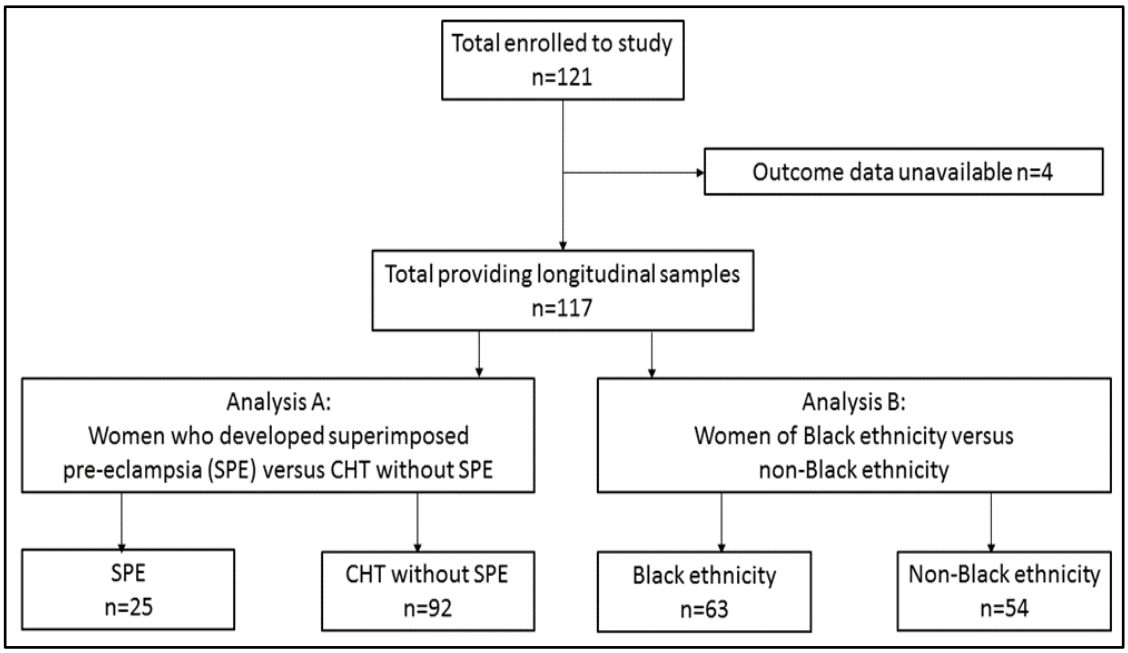


Figure 6.1 Overview flow of study participants including grouping for analyses A and B
CHT= chronic hypertension, SPE=superimposed pre-eclampsia

The baseline demographics of the women who provided samples for the analyses are detailed in Table 6.1. The women who developed superimposed pre-eclampsia, compared to those who did not, were younger (33 years versus 36 years; p 0.04), and a higher proportion of the women who developed superimposed pre-eclampsia, compared to those who did not, had pre-existing diabetes mellitus (24% versus 6.5%; p 0.02). Fewer black women were nulliparous, compared to non-Black women (6.3% versus 33%; p 0.0003), and the diastolic blood pressure was higher in Black women than non-Black women at antenatal booking (88 mmHg versus 85 mmHg; p 0.03). Otherwise the groups were comparable at baseline.

Table 6.1 Baseline demographics for the cohort

Characteristic	All CHT n=117	SPE n=25	CHT without SPE n=92	Black ethnicity n=63	Non-Black ethnicity n=54
Age at study entry, years mean (SD)	35 (5)	33* (6)	36 (5)	36 (5)	35 (6)
Body mass index, Kg/m² mean (SD)	31 (6.2)	31 (5.8)	31 (6.3)	32 (5.5)	30 (6.9)
Nulliparity number (%)	22 (19%)	7 (28%)	15 (16%)	4* (6.3%)	18 (33%)
Smoker number (%)	1 (0.9%)	0	1 (1.1%)	0	1 (1.9%)
Booking blood pressure, mmHg median (IQR)					
Systolic	135 (126 to 142)	134 (127 to 140)	136 (126 to 142)	139 (126 to 147)	134 (126 to 140)
Diastolic	88 (81 to 92)	85 (82 to 90)	88 (81 to 92)	88* (84 to 96)	85 (80 to 90)
Renal disease number (%)	10 (8.5%)	3 (12%)	7 (7.6%)	4 (6.3%)	6 (11%)
Diabetes mellitus number (%)	12 (10%)	6* (24%)	6 (6.5%)	7 (11%)	5 (9.3%)
Centre number (%)					
Guy's and St Thomas' NHS Foundation Trust	73 (62%)	10 (40%)	64 (70%)	48 (76%)	25 (46%)
Central Manchester University Hospitals NHS Foundation Trust	29 (25%)	8 (32%)	21 (23%)	13 (21%)	16 (30%)
University Hospitals of Leicester NHS Trust	15 (13%)	7 (28%)	8 (8.7%)	2 (3.2%)	13 (24%)
Randomised treatment number (%)	94 (80%)	19 (76%)	75 (82%)	52 (83%)	42 (78%)
Labetalol	47 (40%)	6 (24%)	41 (45%)	25 (40%)	22 (41%)
Nifedipine	47 (40%)	13 (52%)	34 (37%)	27 (43%)	20 (37%)

CHT= chronic hypertension, SPE=superimposed pre-eclampsia, SD= standard deviation, IQR= interquartile range

**denotes characteristics that are significantly different between the compared subgroups*

Maternal and perinatal outcomes for the cohort as a whole, in addition to the subgroups within analysis A (superimposed pre-eclampsia versus chronic hypertensive controls) and B (Black women versus non-Black women), are shown in Table 6.2 and 6.3. There were no differences in outcome between labetalol and nifedipine arms of the trial. Superimposed pre-eclampsia was diagnosed in 21% (n=25) of the whole cohort of women with chronic hypertension, with 31% (n=36) of infants being born before 37 weeks' gestation and 91% (n=106) livebirths. Of the 106 livebirths, 29% (n=31) had a birthweight below the 10th centile, 15% (n=16) had a birthweight below the 3rd centile, and 23% (n=25) required admission to the neonatal unit.

Table 6.2 Maternal outcomes

Outcome	All CHT n=117	SPE n=25	CHT without SPE n=92	Black ethnicity n=63	Non-Black ethnicity n=54
Highest blood pressure per woman, mmHg median (IQR)					
Systolic	163 (153 to 172)	173* (167 to 183)	160 (151 to 169)	167 (153 to 176)	159 (154 to 170)
Diastolic	98 (92 to 107)	106* (99 to 112)	97 (90 to 103)	99 (93 to 107)	98 (90 to 104)
Mean blood pressure per woman†, mmHg median (IQR)					
Systolic	133 (127 to 137)	137* (131 to 142)	132 (127 to 136)	134 (127 to 140)	132 (128 to 134)
Diastolic	84 (81 to 89)	87* (84 to 93)	84 (81 to 88)	86* (82 to 90)	83 (81 to 86)
Incidence of severe hypertension‡, days number (%)					
0	44 (38%)	7 (28%)	37 (40%)	20 (32%)	24 (44%)
1	30 (26%)	4 (16%)	26 (28%)	14 (22%)	16 (30%)
2	15 (12%)	1 (4%)	14 (15%)	10 (16%)	5 (9.3%)
≥3	28 (24%)	13* (52%)	15 (16%)	19 (30%)	9 (17%)
Superimposed pre-eclampsia number (%)	25 (21%)	25 (100%)	92 (0%)	9 (14%)	16 (30%)
Mode of delivery number (%)					
Spontaneous vaginal delivery	39 (34%)	4 (16%)	35 (39%)	20 (32%)	19 (35%)
Assisted vaginal delivery	6 (5.2%)	3 (12%)	3 (3.3%)	4 (6.5%)	2 (3.7%)
Elective Caesarean section	16 (14%)	2 (8%)	14 (16%)	6 (9.7%)	10 (19%)
Emergency Caesarean section	54 (47%)	16* (64%)	38 (42%)	32 (52%)	22 (41%)

Gestation at delivery, weeks median (IQR)	38 (35.9 to 39)	34.7* (30.3 to 37.9)	38.3 (37 to 39.3)	37.9 (35.6 to 39)	38.0 (36 to 39.4)
Preterm birth <37 weeks number (%)	36 (31%)	14* (56%)	22 (24%)	19 (30%)	17 (31%)
Perinatal outcome number (%)					
Livebirth	106 (91%)	23 (92%)	83 (91%)	56 (89%)	50 (93%)
Miscarriage	4 (3.4%)	0	4 (4.3%)	3 (4.8%)	1 (1.9%)
Termination of pregnancy	3 (2.6%)	1 (4%)	2 (2.2%)	2 (3.2%)	1 (1.9%)
Stillbirth	4 (3.4%)	1 (4%)	3 (3.2%)	2 (3.2%)	2 (3.7%)

CHT= chronic hypertension, SPE=superimposed pre-eclampsia
**denotes outcomes that are significantly different between the compared groups*
†Mean blood pressure of all antenatal blood pressures during study participation
‡Severe hypertension= systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg

Within the subgroups, the greatest differences in maternal and perinatal outcome were seen in the women with chronic hypertension who developed superimposed pre-eclampsia compared to chronic hypertensive controls. The highest systolic (173 mmHg versus 160 mmHg; p 0.0001), highest diastolic (106 mmHg versus 97 mmHg; p 0.0002), mean systolic (137 mmHg versus 132 mmHg; p 0.005) and mean diastolic (87 mmHg versus 84 mmHg; p 0.002) blood pressures were higher in the women with superimposed pre-eclampsia compared to those with no superimposed pre-eclampsia. Women diagnosed with superimposed pre-eclampsia were more likely to have an emergency Caesarean birth, compared to those without superimposed pre-eclampsia (64% versus 42%; p 0.03). Additionally, preterm birth before 37 weeks' gestation occurred more frequently in women with superimposed pre-eclampsia than without (56% versus 24%; p 0.003). The infants born to mothers who were diagnosed with superimposed pre-eclampsia, compared to those who were not, had lower birthweights (2270g versus 3020g; p <0.0001) and were more likely to be admitted to the neonatal unit (52% versus 14%; p 0.0007). The only significant difference in maternal and perinatal outcome found between the women of Black ethnicity and those of non-Black ethnicity, was higher mean post-enrolment diastolic blood pressure (Black women: 86 mmHg versus non-Black women: 83 mmHg; p 0.03).

Table 6.3 Perinatal outcomes

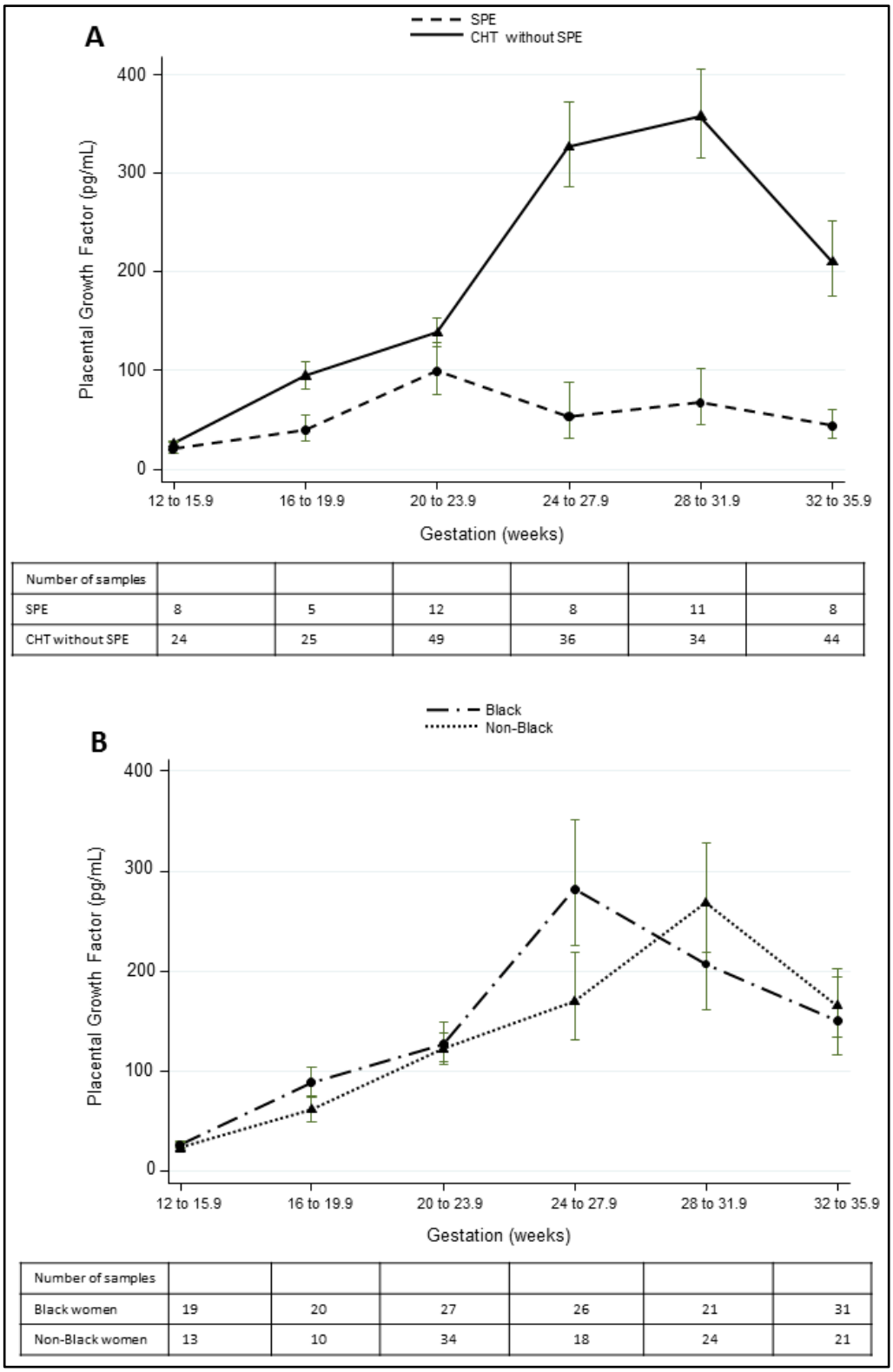
Outcome	All CHT n=106	SPE n=23	CHT without SPE n=83	Black ethnicity n=56	Non-Black ethnicity n=50
Birthweight, g Median (IQR)	2920 (2360 to 3250)	2270* (1320 to 2840)	3020 (2690 to 3440)	2980 (2520 to 3180)	2930 (2560 to 3400)
Birthweight <10th centile number (%)	31 (29%)	13* (52%)	18 (22%)	17 (30%)	14 (28%)
Birthweight <3rd centile number (%)	16 (15%)	10* (40%)	6 (7.2%)	9 (16%)	7 (14%)
Neonatal unit admission number (%)	25 (23%)	12* (52%)	13 (14%)	12 (21%)	13 (26%)

CHT= chronic hypertension, SPE=superimposed pre-eclampsia

**denotes outcomes that are significantly different between the compared groups*

Endothelial biomarkers

The longitudinal changes in PlGF and syndecan-1 are displayed in Figures 6.2, 6.3 and 6.4. Analysis A (superimposed pre-eclampsia versus no superimposed pre-eclampsia) demonstrated that PlGF concentration increased across gestation in both groups (Figure 6.2); however, the PlGF concentrations were 67% lower (95% confidence interval -79% to -48%; p=<0.001) in women who developed superimposed pre-eclampsia compared to those who did not. In analysis B, PlGF concentration increased across gestation in women of Black ethnicity and women of non-Black ethnicity (Figure 6.2). There was no overall difference in concentrations between groups (-2%; 95% confidence interval -43% to 68%; p=0.94).



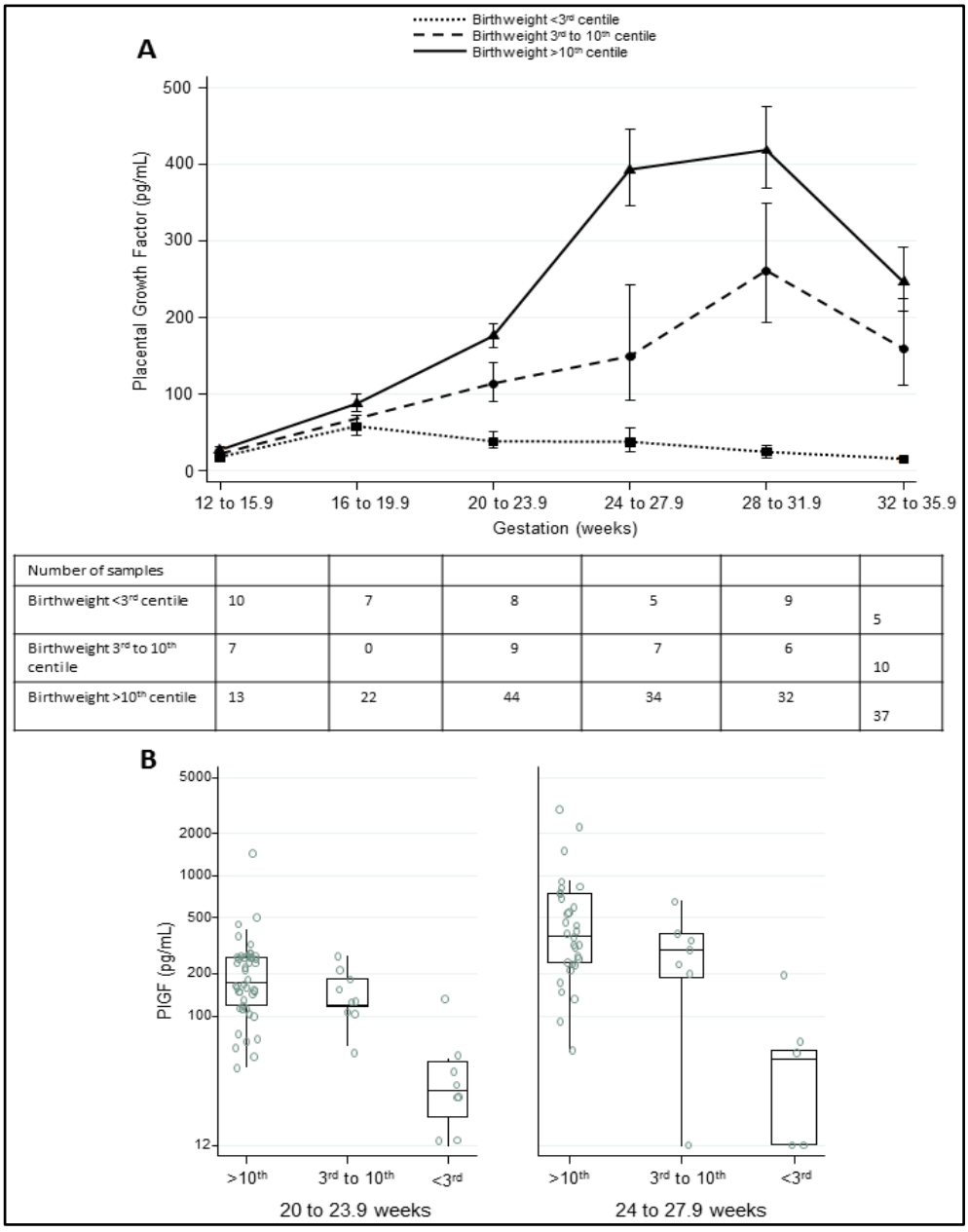
Number of samples						
SPE	8	5	12	8	11	8
CHT without SPE	24	25	49	36	34	44

Number of samples						
Black women	19	20	27	26	21	31
Non-Black women	13	10	34	18	24	21

Figure 6.2 Placental growth factor concentrations across gestation in pregnant women with chronic hypertension.

Comparison A: superimposed pre-eclampsia (SPE) versus no SPE. Comparison B: women of Black ethnicity versus non-Black ethnicity

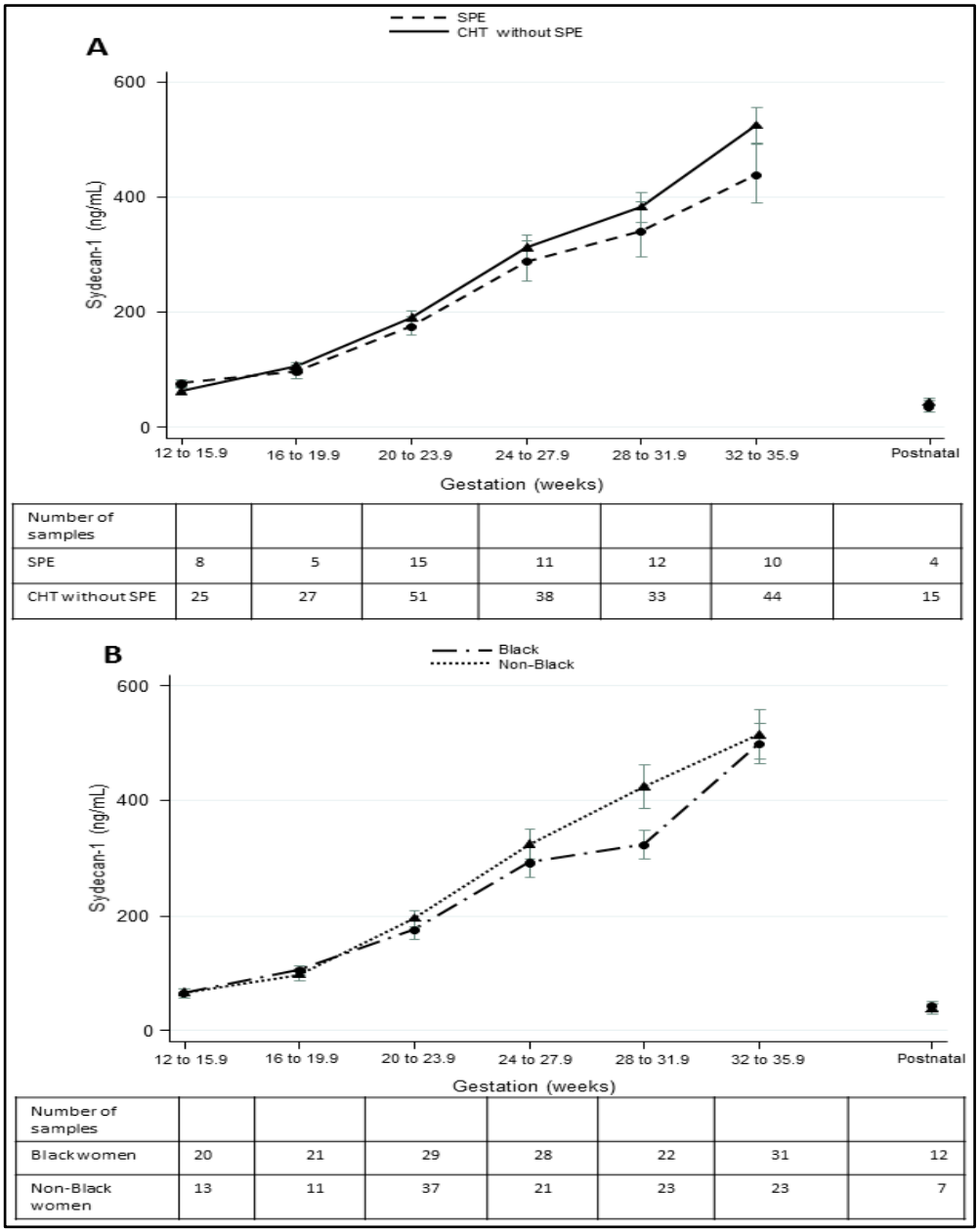
Given the high proportion of infants born below the 3rd and 10th centile in this cohort of women with chronic hypertension, an additional analysis assessed the gestational changes in PlGF by birthweight centile category (<3rd, 3rd to 10th and >10th) (Figure 6.3). PlGF <100 pg/mL at 20 to 23.9 weeks' gestation to predict subsequent birthweight <3rd centile demonstrated 88% sensitivity (95% confidence interval 47% to 100%), 83% specificity (95% confidence interval 70% to 92%), and the negative predictive value was 98% (95% confidence interval 88% to 100%).



Number of samples						
Birthweight <3rd centile	10	7	8	5	9	5
Birthweight 3rd to 10th centile	7	0	9	7	6	10
Birthweight >10th centile	13	22	44	34	32	37

Figure 6.3 Placental growth factor concentration and infant birthweight centile
A: Placental growth factor across gestation in pregnant women with chronic hypertension divided by birthweight centile categories
B: Box plot of placental growth factor concentration at 20 to 23.9 weeks and 24 to 29.9 weeks' gestation divided by infant birthweight centile category

Syndecan-1 concentrations increased significantly across gestation in all subgroups (p <0.0001) (Figure 6.4). Postnatal syndecan-1 concentrations were 83% lower (95% confidence interval -87% to -78%; p=<0.001) than antenatal syndecan-1 concentrations. No significant differences were found in syndecan-1 concentrations either in women with chronic hypertension who did and did not develop superimposed pre-eclampsia (-5%; 95% confidence interval -24% to 18%; p=0.62), or in women with chronic hypertension of Black or non-Black ethnicity (-5%; 95% confidence interval -22% to 15%; p=0.59).



Number of samples							
SPE	8	5	15	11	12	10	4
CHT without SPE	25	27	51	38	33	44	15

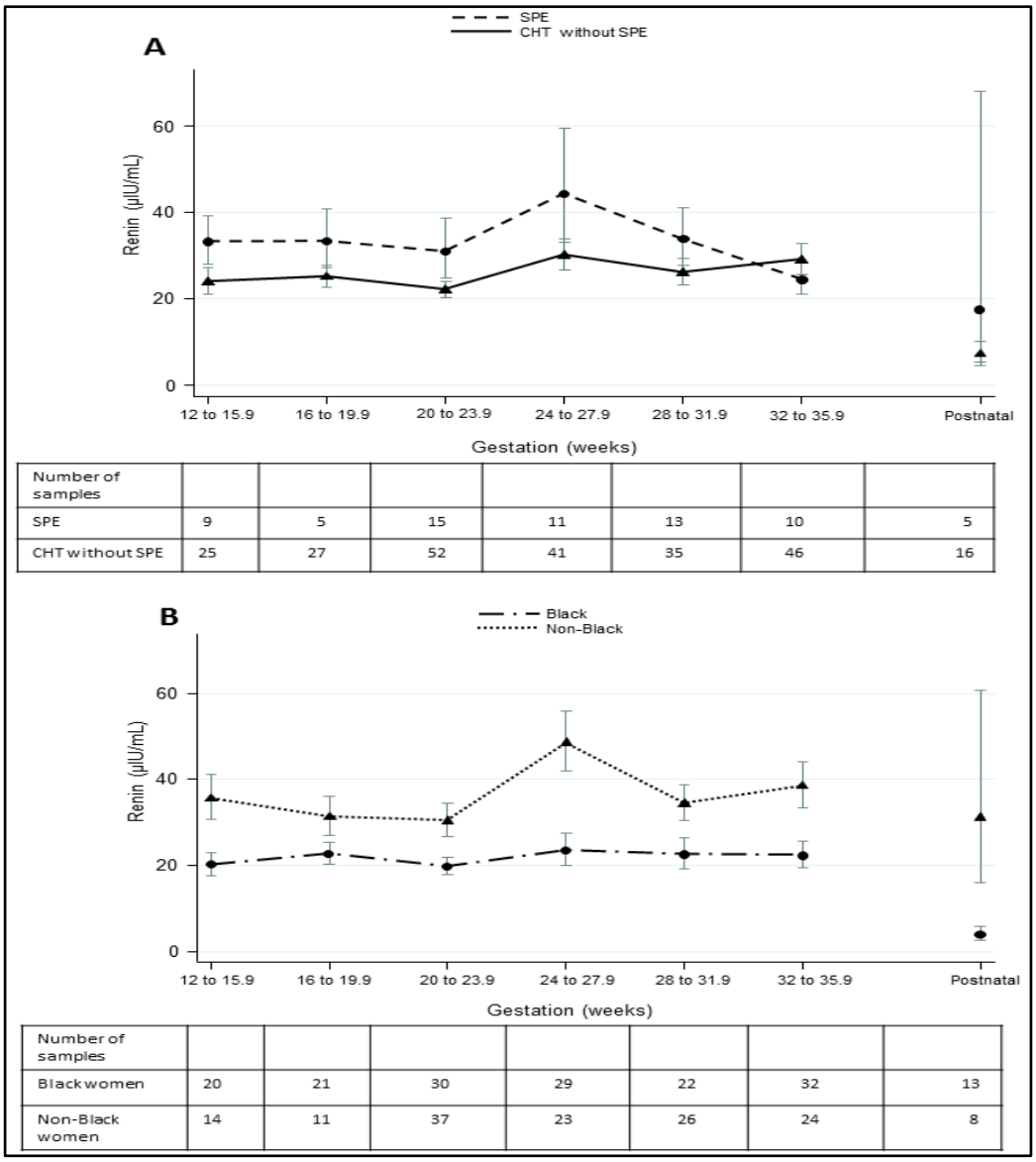
Number of samples							
Black women	20	21	29	28	22	31	12
Non-Black women	13	11	37	21	23	23	7

Figure 6.4 Syndecan-1 concentrations across gestation in pregnant women with chronic hypertension.

Comparison A: superimposed pre-eclampsia (SPE) versus no SPE. Comparison B: women of Black ethnicity versus non-Black ethnicity.

Renal biomarkers

Plasma renin concentrations did not vary significantly over the gestation studied (12 to 35.9 weeks) (Figure 6.5); however antepartum renin concentrations were significantly higher than in samples taken six weeks postnatally ($p < 0.0001$). In the women who developed superimposed pre-eclampsia, the mean renin concentrations at each gestational time point tended to be higher than in women who did not develop superimposed pre-eclampsia until 32 to 35.9 weeks' gestation. However, these differences were not statistically significant when longitudinal measures were compared (34%; 95% confidence interval -2% to 82%; $p=0.06$). In Black women with chronic hypertension with or without superimposed pre-eclampsia, the mean renin concentrations were significantly lower across gestation compared to women of non-Black ethnicity (-43%; 95% confidence interval -58% to -23%; $p=<0.001$). Further analysis explored the differences between gestational renin concentrations and six-week postnatal renin concentrations. In women of Black ethnicity, postnatal renin concentrations were 81% lower (95% confidence interval -91% to -58%; $p=<0.001$) compared with antenatal concentrations and in non-Black women the postnatal renin concentrations were 54% lower (95% confidence interval -73% to -22%; $p=0.004$) than antenatal values in this group. An interaction test examined the potential relationship between ethnicity, gestation and diagnosis of superimposed pre-eclampsia and did not demonstrate a significant correlation.



Number of samples							
SPE	9	5	15	11	13	10	5
CHT without SPE	25	27	52	41	35	46	16

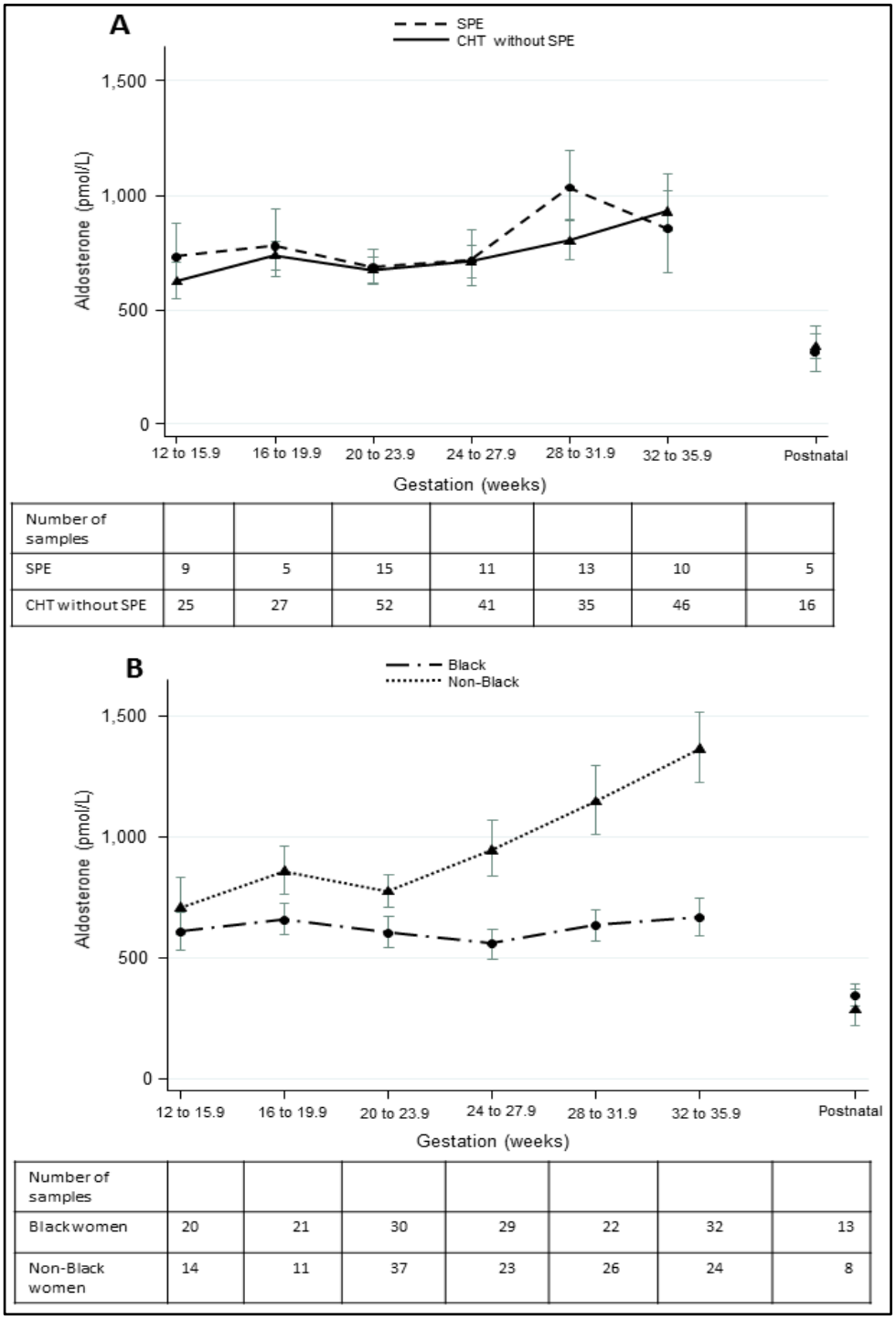
Number of samples							
Black women	20	21	30	29	22	32	13
Non-Black women	14	11	37	23	26	24	8

Figure 6.5 Renin concentrations across gestation in pregnant women with chronic hypertension.

Comparison A: superimposed pre-eclampsia (SPE) versus no SPE. Comparison B: women of Black ethnicity versus non-Black ethnicity.

Aldosterone concentrations were 57% higher (95% confidence interval 43% to 68%; p=<0.001) in pregnancy than at six weeks postpartum. No significant difference was found in aldosterone concentrations between the women who did and did not develop superimposed pre-eclampsia (5%; 95% confidence interval -20% to 39%; p=0.73) (Figure 6.6). In the women of Black ethnicity compared to those of non-Black ethnicity who did or did not develop superimposed pre-eclampsia, aldosterone concentrations in pregnancy were 31% lower (95% confidence interval -45% to -15%; p=0.001). There was no difference in aldosterone concentrations between ethnic groups at the six-week postnatal timepoint (13%; 95% confidence interval -46% to 131%; p=0.72). Across gestation, aldosterone concentrations increased by 70% in the

women of non-Black ethnicity (95% confidence interval 39% to 209%; p=<0.001); however, in the Black women no significant increase in aldosterone concentrations was demonstrated across gestation (13%; 95% confidence interval -7% to 37%; p=0.23). An interaction test explored the potential association of ethnicity, gestation and diagnosis of superimposed pre-eclampsia and did not demonstrate a significant correlation.

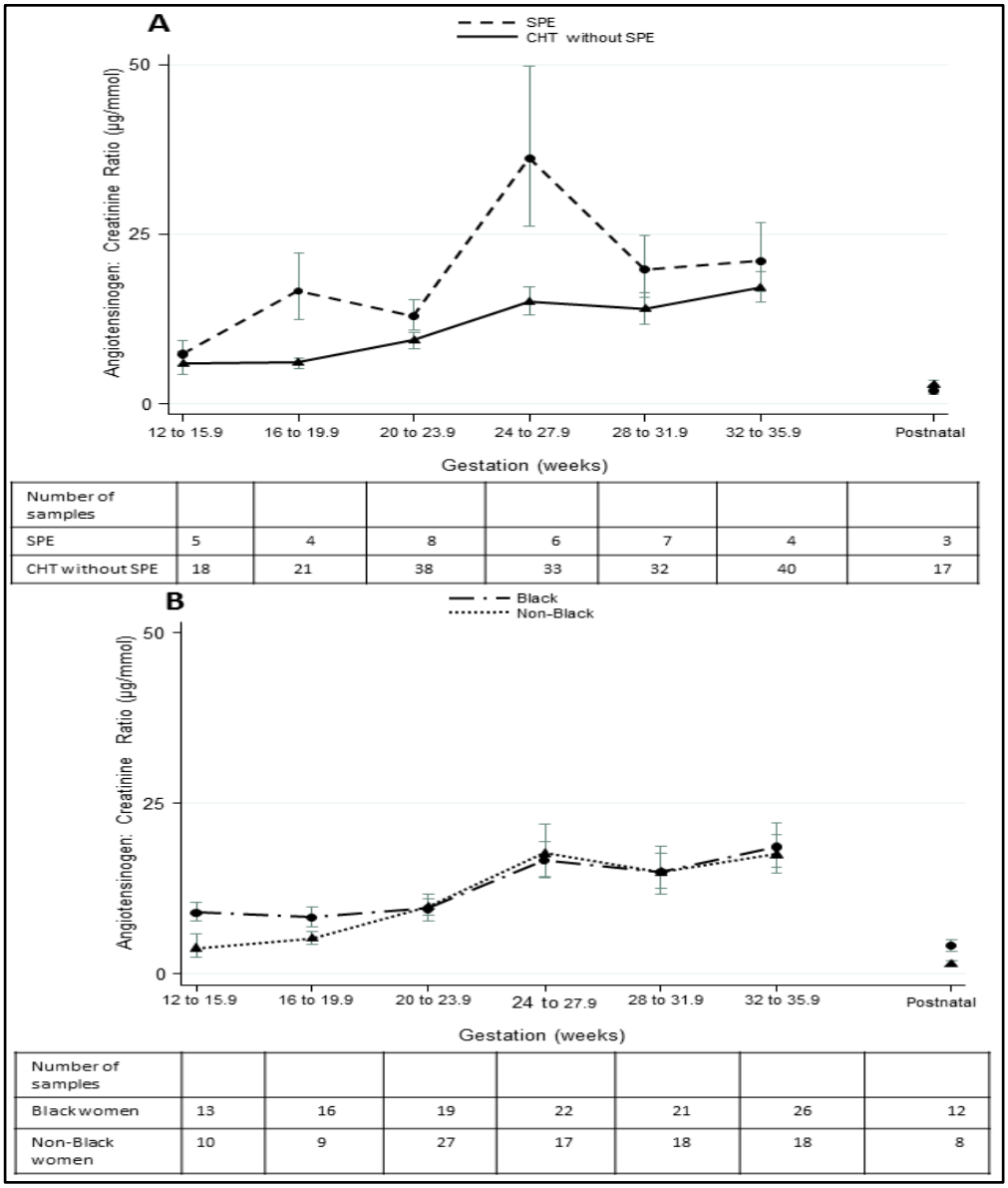


Number of samples							
SPE	9	5	15	11	13	10	5
CHT without SPE	25	27	52	41	35	46	16

Number of samples							
Black women	20	21	30	29	22	32	13
Non-Black women	14	11	37	23	26	24	8

Figure 6.6 Aldosterone concentrations across gestation in pregnant women with chronic hypertension.
Comparison A: superimposed pre-eclampsia (SPE) versus no SPE. Comparison B: women of Black ethnicity versus non-Black ethnicity.

Urinary AGTCR increased across gestation and was significantly lower at six weeks postpartum (-79%; 95% confidence interval -86% to -69%; p=<0.001). In the women with superimposed pre-eclampsia, compared to chronic hypertensive controls, the AGTCR was 63% higher across gestation (95% confidence interval 10% to 142%; p=0.02) (Figure 6.7). There was no difference between the AGTCR in women of Black or non-Black ethnicity (12%; 95% confidence interval -22% to 61%; p=0.53). No correlation between the systemic RAAS (plasma renin and aldosterone) or the intra-renal RAS (AGTCR) was found.

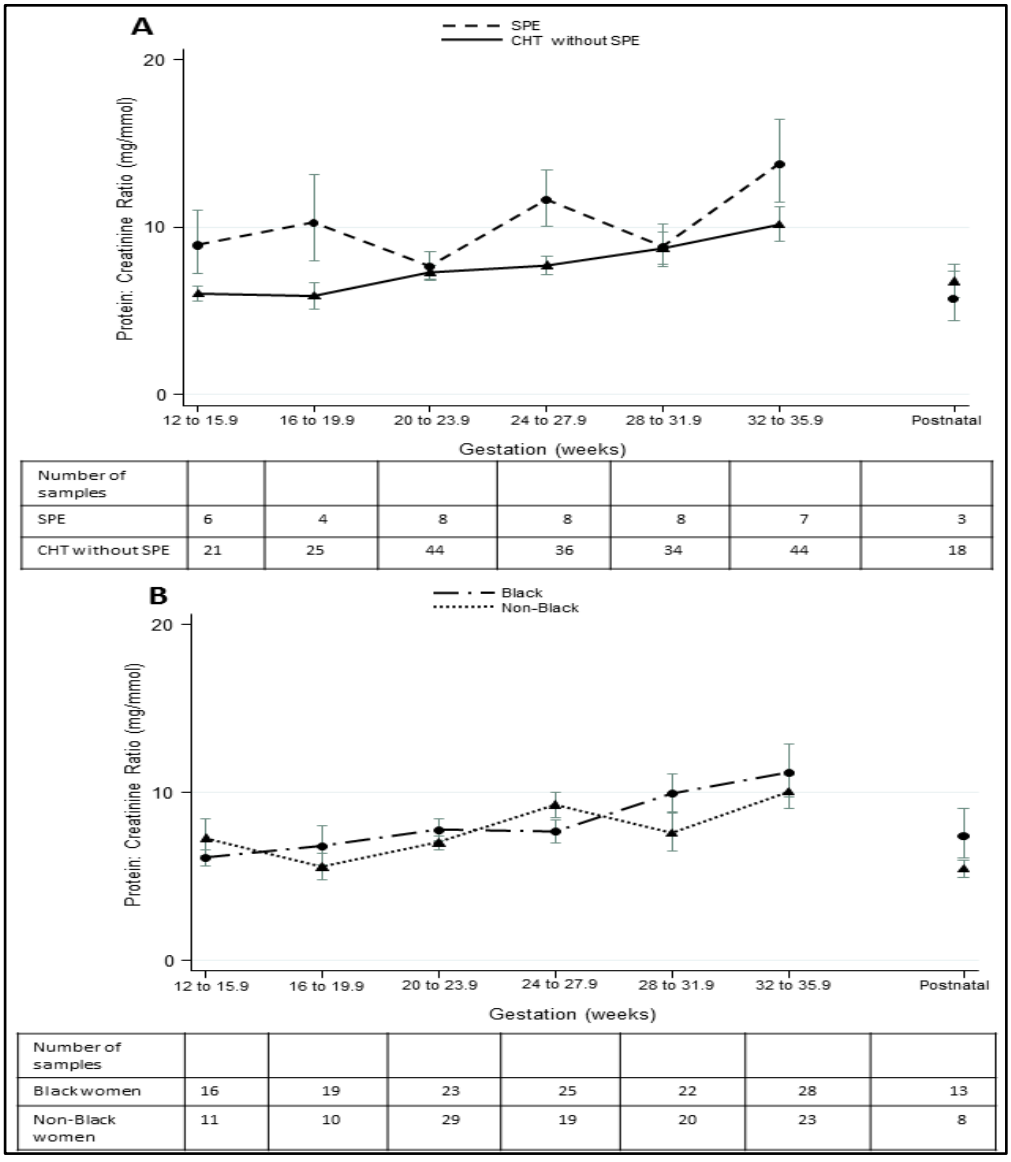


Number of samples							
SPE	5	4	8	6	7	4	3
CHT without SPE	18	21	38	33	32	40	17

Number of samples							
Black women	13	16	19	22	21	26	12
Non-Black women	10	9	27	17	18	18	8

Figure 6.7 Urinary angiotensinogen: creatinine concentrations across gestation in pregnant women with chronic hypertension.
Comparison A: superimposed pre-eclampsia (SPE) versus no SPE. Comparison B: women of Black ethnicity versus non-Black ethnicity.

PCR increased across gestation in all subgroups (51%; 95% confidence interval 24% to 84%; p=<0.001) and returned to levels comparable to the 12 to 16.9 week mean ratio by six weeks postpartum. PCR was overall significantly higher across gestation in the women who subsequently developed superimposed pre-eclampsia compared to those who did not (29%; 95% confidence interval 5% to 57%; p=0.01) (Figure 6.8). There was no significant difference in PCR across gestation in Black and non-Black women (4%; 95% confidence interval -14% to 24%; p=0.71).

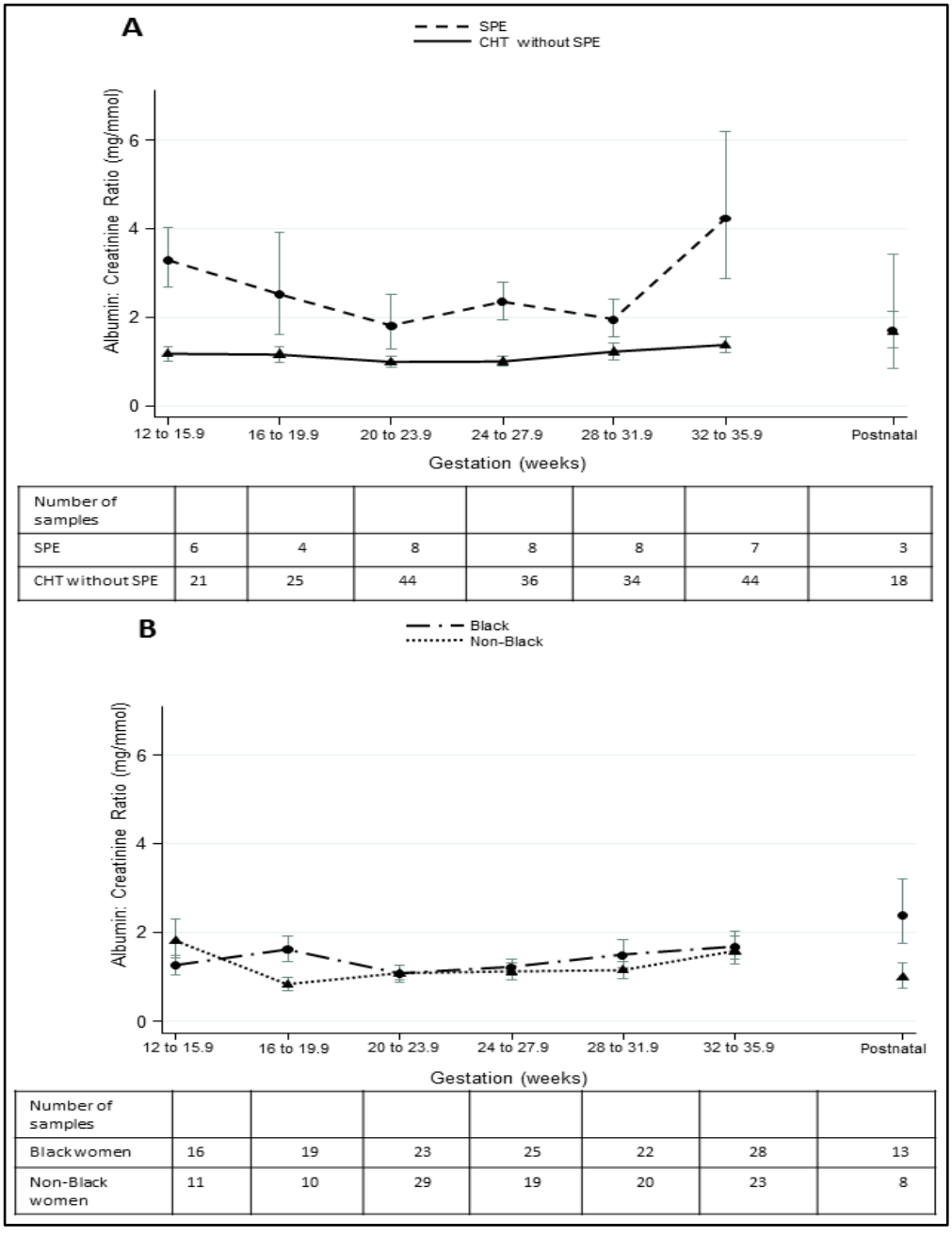


Number of samples							
SPE	6	4	8	8	8	7	3
CHT without SPE	21	25	44	36	34	44	18

Number of samples							
Black women	16	19	23	25	22	28	13
Non-Black women	11	10	29	19	20	23	8

Figure 6.8 Urinary protein: creatinine ratio concentrations across gestation in pregnant women with chronic hypertension.
Comparison A: superimposed pre-eclampsia (SPE) versus no SPE. Comparison B: women of Black ethnicity versus non-Black ethnicity.

ACR did not vary significantly across gestation in the cohort as a whole (20%; 95% confidence interval -10% to 59%; p=0.22). However, in the women who were subsequently diagnosed with superimposed pre-eclampsia compared to chronic hypertensive controls, ACR was higher (123%; 95% confidence interval 67% to 197%; p=<0.001) (Figure 6.9). There was no difference in ACR when women of Black and non-Black ethnicity were compared (10%; 95% confidence interval -19% to 50%; p=0.55).



Number of samples							
SPE	6	4	8	8	8	7	3
CHT without SPE	21	25	44	36	34	44	18

Number of samples							
Black women	16	19	23	25	22	28	13
Non-Black women	11	10	29	19	20	23	8

Figure 6.9 Urinary albumin: creatinine ratio concentrations across gestation in pregnant women with chronic hypertension.

Comparison A: superimposed pre-eclampsia (SPE) versus no SPE. Comparison B: women of Black ethnicity versus non-Black ethnicity.

6.5 Discussion

This study has confirmed that low PlGF across gestation in women with chronic hypertension in pregnancy predates the clinical presentation of superimposed pre-eclampsia and fetal growth restriction. To our knowledge, this is the first study in women with chronic hypertension to demonstrate the potential utility of PlGF as a predictive tool for fetal growth restriction; with further validation, PlGF concentrations <100 pg/mL at 20 to 23.9 weeks' gestation may aid risk stratification and timing of ultrasound surveillance in this group. The high incidence of adverse maternal and perinatal outcomes in women with chronic hypertension in pregnancy is highlighted by this study with 21% of women developing superimposed pre-eclampsia, comparable with the findings of other studies ranging from 17 to 25%.[7,30,46,53] Women with chronic hypertension who did not develop superimposed pre-eclampsia were also at increased risk of adverse perinatal outcome compared to background incidence, but a significantly greater proportion of adverse perinatal outcomes were seen in the women who developed superimposed pre-eclampsia.

Syndecan-1 is a transmembrane heparin sulphate proteoglycan expressed on the extracellular, luminal surface of epithelial cells and syncytiotrophoblasts, forming part of the glycocalyx of these cells. Syndecan-1 is involved in the regulation of cell adhesion, proliferation, motility, intra-cellular signalling and angiogenesis.[205] Our findings confirm circulating syndecan-1 concentrations increase across gestation as previously demonstrated;[207] however in this study syndecan-1 concentrations did not differ significantly in women with chronic hypertension who developed subsequent superimposed pre-eclampsia compared with chronic hypertensive controls. This finding is in contrast to results reported by Gandley and colleagues (2016) who reported that plasma syndecan-1 concentrations at 20 weeks' gestation were significantly lower in women who developed subsequent pre-eclampsia (174 ng/mL versus 272 ng/mL; $p < 0.05$).[207] Further exploration of the role of syndecan-1 in the pathophysiology of placental disease in different populations is required to determine the clinical utility of this biomarker.

The role of the systemic RAAS in the pathophysiology of placental disease in women with chronic hypertension in pregnancy is unclear. No significant variation in plasma renin or aldosterone concentrations were found across gestation in the women who did and did not develop superimposed pre-eclampsia. Previous studies have demonstrated that the RAAS is upregulated in normotensive pregnancy and our study confirms that this upregulation occurs in both the Black and non-Black women with chronic hypertension, though it is unclear if this is in response to, or the cause of other physiological changes that occur in pregnancy such as

increased plasma volume and vasodilation.[103] Brown and colleagues (1997) performed a cross-sectional study and found that women diagnosed with pre-eclampsia had lower plasma concentrations of renin and aldosterone compared to normotensive pregnant women.[354] Another longitudinal study by August and colleagues (1990) in 25 pregnant women with chronic hypertension, demonstrated reduced plasma renin activity and lower urinary aldosterone concentrations in those who developed subsequent superimposed pre-eclampsia compared to those who did not.[109] Importantly our study confirms that systemic renin and aldosterone concentrations in Black women with chronic hypertension are lower across gestation compared to non-Black women in keeping with the non-pregnant state, and any future investigation of the role of the systemic RAAS in pregnancy should account for this ethnic variation.

It is interesting that although there is variation in the systemic RAAS between ethnic groups, no variation in the intrarenal RAS was observed, nor was any relationship between systemic and intrarenal identified. This is in keeping with the findings of other studies outside pregnancy that suggest that in individuals with low-renin hypertension, in whom intrarenal RAS is active, independently of systemic RAAS and may play a role in the pathogenesis of hypertensive nephropathy.[218] Increased urinary AGTCR were found across gestation in women who developed superimposed pre-eclampsia compared to those who did not. Pathological upregulation of the intrarenal RAS in pre-eclampsia would be consistent with findings outside pregnancy; an activated intrarenal RAS has been reported in the progression of renal injury in diabetic and membranous nephropathy.[219] However, our findings do not agree with a cross-sectional study reported by Yilmaz and colleagues (2009), who compared time-of-disease AGTCR in 30 women with pre-eclampsia with 30 normotensive pregnant women. They found that urinary AGTCR were lower in women with pre-eclampsia.[357] This study did, however, report a positive correlation between urinary AGTCR, high blood pressure and proteinuria, and concluded that 'local RAS activation in the kidneys may be one of the contributing factors in the development of pre-eclampsia'.[357] In this respect our findings concur, but further investigation is required to establish the importance of the intrarenal RAS in the pathophysiology of superimposed pre-eclampsia.

PCR and ACR were higher across gestation in women with chronic hypertension who developed subsequent superimposed pre-eclampsia compared to those who did not. This may represent underlying nephropathy in this group of women with chronic hypertension, as

described by Crews and colleagues (2010).[224] However, another study by Poon and colleagues (2008) found higher first trimester ACR was associated with subsequent development of pre-eclampsia,[358] so it may be that the association of higher PCR/ACR from the first trimester is indicative of endothelial dysfunction with subsequent development of superimposed pre-eclampsia. The clinical utility of these findings are unclear, as proteinuria is known to increase in normotensive pregnancy and identifying when protein excretion is abnormal is problematic.[221,226] It is also notable that the mean PCR and ACR values across gestation in the women in our cohort who developed subsequent superimposed pre-eclampsia were below 30 mg/mmol and 8 mg/mmol respectively (prior to diagnosis), which are currently utilised for clinical diagnosis.[21]

In this study, the proportion of the Black women developing superimposed pre-eclampsia was lower than the proportion of non-Black women (14% versus 30%; p=0.07), though this was not significant and may relate in part to the higher proportion of multiparous women in the Black group. The significant difference in booking and mean post-enrolment diastolic blood pressures in women of Black ethnicity, compared to non-Black, suggests potential ethnic variation in disease severity, which has been demonstrated in the non-pregnant population.[359-361] Variation in the systemic RAAS may play a role in ethnic disparity in disease severity. Our study has highlighted differences in the RAAS, in particular a third trimester increase in aldosterone concentrations that is present in the non-Black women, but not in the Black women and these findings warrant further exploration.

The strengths of this study include multicentre recruitment of a wide ethnic mixture of women with chronic hypertension in pregnancy. Longitudinal sampling has allowed assessment of variation of biomarkers across gestation prior to development of adverse outcome. In contrast, a limitation of the study was the absence of time-of-disease sampling, preventing comparison of each biomarker at the time of clinical diagnosis of superimposed pre-eclampsia, and the findings of this study would require validation in a much larger cohort. Future research should aim to examine longitudinal and time of disease biomarker concentrations, with simultaneous quantification of other biomarkers that are involved in pathophysiological pathways such as the RAAS. This would provide further explanation of the mechanisms underpinning increased adverse maternal and perinatal outcome in pregnant women with chronic hypertension.

Changes in placental and renal biomarkers predate development of superimposed pre-eclampsia. Low plasma PlGF has a strong association with subsequent fetal growth restriction in women with chronic hypertension and ethnic variation in RAAS biomarkers may relate to disparity in outcome. Further research into the physiology underpinning these differences is warranted.

CHAPTER 7 LONGITUDINAL CHANGES IN VASCULAR FUNCTION PARAMETERS IN PREGNANT WOMEN WITH CHRONIC HYPERTENSION AND ASSOCIATION WITH ADVERSE OUTCOME: A COHORT STUDY

7.1 Abstract

Increased vascular function measures such as central aortic pressure (CAP), pulse wave velocity (PWV) and augmentation index (AIX) are associated with cardiovascular morbidity in the non-pregnant population. These haemodynamic parameters may also change in pregnancy prior to development of adverse maternal and perinatal outcomes. The aim of this study was to evaluate the association between longitudinal vascular function parameters and adverse outcomes in pregnant women with chronic hypertension. Pregnant women recruited to the PANDA (Pregnancy And chronic hypertension: NifeDipine versus lAbetalol as antihypertensive treatment) study in three UK maternity units had serial pulse wave analyses performed using the Arteriograph® (Tensiomed, Budapest, Hungary) while in a sitting position. Brachial systolic (SBP) and diastolic blood pressure (DBP), CAP, AIX, and PWV were measured across gestation from 12 weeks onwards. AIX was additionally adjusted for a heart rate of 75 beats per minute (AIX-75). Statistical analysis used random-effects logistic regression models and compared those who developed superimposed pre-eclampsia (SPE) to those who did not, women who delivered a small for gestational age infant (<10th birthweight centile) (SGA10) to those who delivered an infant with birthweight >10th centile, and women of Black ethnicity with women of non-Black ethnicity. The cohort included 97 women (57% (n=55) of Black ethnicity) with chronic hypertension and singleton pregnancies. SPE was diagnosed in 18% (n=17) and 30% (n=29) of infants were SGA10. In women who developed subsequent SPE compared to those who did not, brachial SBP (148 versus 139 mmHg; p=0.002), DBP (87 versus 82 mmHg; p=0.01), CAP (139 versus 128 mmHg; p=0.001) and AIX-75 (29 versus 22%; p=0.01) were all higher across gestation. Brachial SBP (146 versus 138 mmHg; p=0.001), DBP (86 versus 82 mmHg; p=0.01), CAP (137 versus 127 mmHg; p=<0.0001), and PWV (9.1 versus 8.5 m/s; p=0.02) were higher across gestation in women who delivered an SGA10 infant compared to women who delivered an infant with birthweight >10th centile. No longitudinal differences were found in the vascular function parameters in women of Black ethnicity compared to non-Black ethnicity. Variation in vascular function parameters and brachial blood pressure exist longitudinally in pregnant women with chronic hypertension who develop adverse maternal and perinatal outcome. Further investigation of the potential clinical utility of these findings is warranted.

7.2 Introduction

Pulse wave analysis is a non-invasive technique that utilises the peripheral pressure waveforms, and generation of the corresponding central waveform, to derive vascular function measures, such as central aortic pressure (CAP), augmentation index of the aorta (AIX), and pulse wave velocity of the aorta (PWV). These parameters are considered markers of arterial stiffness and, in the non-pregnant population, are associated with an increased risk of cardiovascular disease.[240,241,362] There is also evidence that these measures may change in pregnancy prior to development of adverse outcomes such as pre-eclampsia.[252,253] Increased brachial blood pressure is associated with subsequent adverse perinatal outcome. A recent post-hoc analysis of the Control of Hypertension In Pregnancy Study (CHIPS) (2016) demonstrated that severe hypertension was associated with an increased risk of superimposed pre-eclampsia (SPE) (odd ratio 6.09; 95% confidence interval 4.37 to 8.49) and small for gestational age infants (<10th birthweight centile- SGA10) (odds ratio 2.06; 95% confidence interval 1.44 to 2.96).[133]

Chronic hypertension complicates 3% of pregnancies.[7,30] The risk of adverse maternal and perinatal outcomes in women with chronic hypertension, such as SPE[8,29,45] and fetal growth restriction[8,54], are increased compared to the general pregnant population. The increased maternal vascular resistance and decreased maternal vascular compliance that is associated with chronic hypertension may cause maladaptation of the maternal circulation to the physiological demands of pregnancy.[110,308] However the mechanisms underpinning these differences in outcome in women with chronic hypertension in pregnancy are likely to be multifactorial and are currently poorly understood. Previous studies have demonstrated an association between the diagnosis of pre-eclampsia and subsequent increased risk of cardiovascular morbidity and mortality.[140,363] Investigation of arterial stiffness parameters in women with chronic hypertension in pregnancy may offer some insight into the mechanism behind this increased risk.

Previous studies have demonstrated an association between Black ethnicity and adverse pregnancy outcome.[313-315,329] Prevalence of chronic hypertension is higher at a younger age among Black women, compared to White women,[25,27] and Black ethnicity, compared to White, is associated with an increased lifetime risk of cardiovascular morbidity and mortality.[364,365] A sub-analysis of the women with chronic hypertension who participated in the Vitamin In Pregnancy trial demonstrated an association between Black ethnicity (compared to White) and development of SPE (adjusted odds ratio 2.31; 95% confidence interval 1.47 to 3.63).[45] Ethnic

variation in vascular function parameters has been demonstrated in the non-pregnant population; Black individuals aged 20 to 70 years had increased AIX compared with those who were White (21 versus 18%; p=0.001) and PWV (7.4 versus 7.1 m/s; p=0.001).[366] Exploration of the impact of ethnicity on pulse wave analyses in pregnancy complicated by chronic hypertension may provide insight into pathophysiological mechanisms underpinning ethnic differences in pregnancy outcome.

This study aimed to investigate longitudinal variation in vascular function parameters, using pulse wave analysis, in women with chronic hypertension in pregnancy, to establish the impact of ethnicity, SPE and SGA10 on these measures.

7.3 Methods

This was a nested cohort study of women with chronic hypertension who participated in the PANDA (Pregnancy And chronic hypertension: NifeDipine versus lAbetalol as antihypertensive treatment) study between 2014 and 2016. The PANDA study was primarily a randomised controlled feasibility study comparing labetalol and nifedipine for control of chronic hypertension in pregnancy (demonstrating comparable effectiveness of both agents at controlling blood pressure to treatment target across gestation), but women who were ineligible for randomisation (due to medication contraindication) or declined randomisation were recruited to an observational arm of the study. The study was registered with ISRCTN (DOI 10.1186/ISRCTN40973936, www.isrctn.com) and approved by the UK Research Ethics Committee (REC number 13/EE/0390). The study has been reported in line with STROBE guidance for reporting of cohort studies.[325]

Study Design

Women were enrolled at three consultant-led National Health Service (NHS) obstetric units in the United Kingdom (Guy's and St Thomas' NHS Foundation Trust, Central Manchester University NHS Foundation Trust, and St George's University Hospitals NHS Foundation Trust). The eligibility criteria included women with a prenatal diagnosis of chronic hypertension or blood pressure readings ≥140/90 mmHg prior to 20 weeks' gestation requiring antihypertensive treatment, as defined by the International Society for the Study of Hypertension in Pregnancy classification of hypertensive disorders of pregnancy,[21] between 12 and 27.9 weeks' gestation, singleton pregnancies, aged over 18 years, and with ability to provide informed consent. Longitudinal vascular function of the study participants was measured using pulse wave analysis. Baseline demographic and antenatal booking data were

collected at enrolment. Ethnicity (Black versus non-Black) was determined by whether the woman had a parent or grandparent who was African or Caribbean by self-report. Clinical blood pressure readings taken at all subsequent antenatal visits (using automated and manual blood pressure devices) and daily during hospital admissions (highest of that day) were recorded in addition to other maternal and perinatal outcome data (SPE, mode of delivery, gestation at delivery, pregnancy loss, birthweight, birthweight centile and neonatal unit admission). SPE was defined as new-onset proteinuria, a sudden increase in proteinuria if already present in early gestation, and an increase in hypertension, as recommended by the American College of Obstetrics and Gynaecology practice bulletin.[343] Customised birthweight centiles were calculated using the GROW formula with adjustment for maternal height, maternal weight, maternal ethnicity, parity, infant sex, infant birthweight and gestation at birth (version 6.7.5.1 (2014)).[322] Infant birthweight below the 10th centile was considered diagnostic of small for gestational age (SGA10).

Pulse Wave Analysis

Pulse wave analyses were obtained using the Arteriograph® (Tensiomed, Budapest, Hungary), an oscillometric single-cuff device. Readings were obtained at study enrolment, 20 weeks, 28 weeks, and 34 weeks' gestation (+/- two weeks). All pulse wave measurements were performed with participants in the sitting position. The Arteriograph® cuff was applied to the left arm over the brachial artery for estimation of CAP (mmHg), PWV (m/s) and AIX (%).The AIX was also converted to an additional vascular function parameter AIX-75, adjusting for a heart rate of 75 beats per minute as previously described by Khalil and colleagues (2012).[231] The device additionally recorded brachial SBP and DBP (mmHg). All recordings were made by researchers who had received appropriate training on the use of the Arteriograph®. The results of the pulse wave analyses were not given to the women or their doctors and did not influence the subsequent management of the pregnancies.

Statistical Analysis

The statistical software Stata version 14 (StataCorp, College Station, Texas) and GraphPad Prism 7 (Graph Pad Software, San Diego, California) were used for all analyses. The investigation was divided into three parts. Baseline characteristics, clinical brachial blood pressure measurements, clinical outcomes and longitudinal vascular function parameters were compared between women with chronic hypertension who developed SPE and women with chronic hypertension who did not develop SPE (analysis A), women with chronic hypertension

who gave birth to an SGA10 infant with women with chronic hypertension who gave birth to an infant with a birthweight >10th centile (analysis B) and Black women with chronic hypertension with non-Black women with chronic hypertension (analysis C).

Baseline characteristics and clinical outcomes were compared between subgroups using t-tests or Mann-Whitney test for continuous variables depending on the distributions and Fisher's exact test or Chi-squared test for categorical variables. The mean and standard deviation (SD) of each vascular function parameter within each comparison was calculated. Variation in longitudinal vascular function measurements was assessed in each comparative analysis (A, B and C) using random effects regression models allowing for gestation effects, which provided adjusted mean differences with 95% confidence intervals for each analysis. Further investigation of the data included the comparison of clinical brachial systolic and diastolic blood pressures in analysis A, B and C.

7.4 Results

The total number of women enrolled into this cohort study was 106 (Figure 7.1 details flow of study participants). Of these, four (3.8%) withdrew or were lost to follow-up, and five (4.7%) were excluded from the analysis as they had a second trimester pregnancy loss. Longitudinal vascular function assessments (290 in total) were obtained in 97 women (92%). Of the 290 readings obtained, 16 (5.5%) did not provide an AIX or PWV value and eight (2.9%) of the readings with AIX and PWV could not be included in the analyses of these parameters, as the standard deviation of the pulse wave was greater than the pre-specified 1.5 cut-off. For analysis A the cohort was divided into women diagnosed with SPE (n=17) and compared with women who were not diagnosed with SPE (n=80), for analysis B women with infants born below the 10th birthweight centile (n=29) were compared with women with infants born above the 10th birthweight centile (n=68), and for analysis C the cohort was divided into women of Black ethnicity (n=55) versus women self-identifying as of non-Black ethnicity (n=42). The results are presented with summary tables for comparisons of the vascular function variables within each of the three analyses (Tables 7.4, 7.5 and 7.6), but the figures are collated by vascular function variable across the three analyses (A, B and C) to allow visual comparison of the longitudinal variation and inter-relationship between analyses (Figures 7.2 to 7.7).

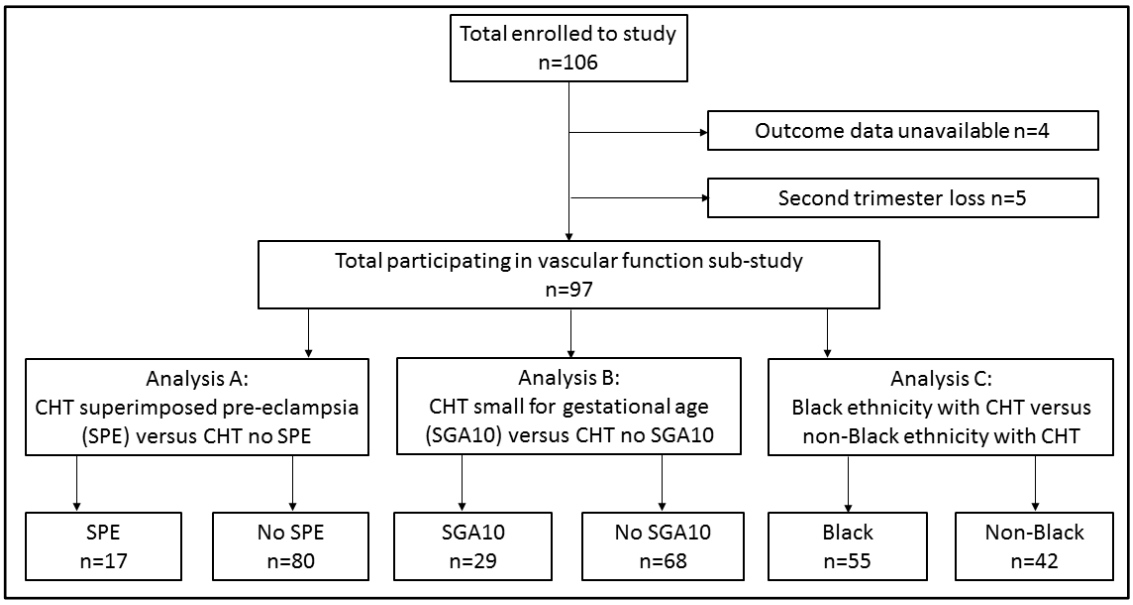


Figure 7.1 Overview flow of study participants including grouping for analyses A, B and C
CHT= chronic hypertension, SPE=superimposed pre-eclampsia, SGA10=neonates with birthweight below the 10th centile
Participants of vascular function sub-study only presented in this schematic.

The baseline demographics of the cohort are detailed in Table 7.1. Body mass index was higher in the Black women compared to the non-Black women (32 kg/m^2 versus 29 kg/m^2; p=0.02). There was a lower proportion of nulliparous women in the group of Black ethnicity compared to non-Black ethnicity (3.6% versus 31%; p=<0.0001), and the median antenatal booking SBP was higher in the women of Black ethnicity compared to the women of non-Black ethnicity (140 mmHg versus 134 mmHg; p=0.02). Otherwise baseline characteristics were comparable between subgroups.

Table 7.1 Baseline demographics for the cohort

Characteristic	All CHT n=97	SPE n=17	CHT no SPE n=80	Black ethnicity n=55	Non-Black ethnicity n=42
Age at study entry, years mean (SD)	35 (6)	34 (6)	35 (5)	35 (5)	35 (6)
Body mass index, Kg/m^2 mean (SD)	31 (5.7)	31 (4.6)	30 (6.0)	32* (5.6)	29 (6.5)
Nulliparity number (%)	15 (15%)	4 (24%)	11 (14%)	2* (3.6%)	13 (31%)
Smoker number (%)	1 (1.0%)	0	1 (1.3%)	0 (0%)	1 (2.4%)
Booking blood pressure, mmHg median (IQR)					
Systolic	136 (126 to 142)	138 (130 to 142)	136 (125 to 143)	140* (128 to 148)	134 (125 to 140)
Diastolic	88 (80 to 92)	84 (80 to 89)	88 (80 to 92)	88 (80 to 92)	84 (80 to 90)
Centre number (%)					
Guy's and St Thomas' NHS Foundation Trust	54 (56%)	6 (35%)	48 (60%)	35 (64%)	19 (45%)
Central Manchester University Hospitals NHS Foundation Trust	32 (33%)	9 (53%)	23 (29%)	14 (25%)	18 (43%)
St George's University Hospitals NHS Foundation Trust	11 (11%)	2 (12%)	9 (11%)	6 (11%)	5 (12%)
Randomised to antihypertensive treatment number (%)	87 (90%)	16 (94%)	71 (89%)	50 (91%)	37 (88%)
Labetalol	45 (47%)	6 (35%)	39 (49%)	26 (47%)	19 (45%)
Nifedipine	42 (43%)	10 (59%)	32 (40%)	24 (44%)	18 (43%)

CHT= chronic hypertension, SPE=superimposed pre-eclampsia, SD= standard deviation, IQR= interquartile range

**denotes characteristics that are significantly different between the compared subgroups (p=<0.05)*

Adverse maternal and perinatal outcomes were common in the cohort as a whole (Tables 7.2 and 3), with 18% (n=17) of women developing SPE in their pregnancy, 63% (n=61) of women requiring a Caesarean birth, 24% (n=23) of births occurring before 37 weeks' gestation, and 3.1% (n=3) stillbirths. Other adverse neonatal outcomes included 30% (n=29) SGA10, 14% (n=14) of infants with birthweight <3rd centile, and 22% (n=21) required admission to the neonatal unit. There were no significant differences in maternal and perinatal outcomes between the women of Black ethnicity and non-Black ethnicity (Table 7.2 and 7.3).

Table 7.2 Maternal outcomes of the cohort

Outcome	All CHT n=97	SPE n=17	CHT no SPE n=80	Black ethnicity n=55	Non-Black ethnicity n=42
Highest blood pressure per woman, mmHg median (IQR)					
Systolic	162 (151 to 174)	180* (166 to 189)	160 (150 to 169)	167 (153 to 175)	158 (150 to 171)
Diastolic	98 (91 to 106)	107* (98 to 116)	97 (90 to 103)	100 (92 to 107)	96 (90 to 104)
Superimposed pre-eclampsia number (%)	17 (18%)	17 (100%)	0 (0%)	7 (13%)	10 (24%)
Mode of delivery number (%)					
Spontaneous vaginal delivery	31 (32%)	2 (12%)	29 (36%)	16 (29%)	15 (36%)
Assisted vaginal delivery	5 (5.2%)	2 (12%)	3 (3.8%)	4 (7.3%)	1 (2.4%)
Elective Caesarean section	17 (18%)	0 (0%)	17 (21%)	9 (16%)	8 (19%)
Emergency Caesarean section	44 (45%)	13* (76%)	31 (39%)	26 (47%)	18 (43%)
Gestation at delivery, weeks median (IQR)	38 (37 to 39.3)	33* (30.3 to 36.4)	39 (37.8 to 39.3)	38 (37.2 to 39.3)	38 (36.4 to 39.2)
Preterm birth <37 weeks number (%)	23 (24%)	13* (76%)	10 (13%)	11 (20%)	12 (29%)
Perinatal outcome number (%)					
Livebirth	94 (97%)	17 (100%)	77 (96%)	54 (98%)	40 (95%)
Stillbirth	3 (3.1%)	0 (0%)	3 (3.8%)	1 (1.8%)	2 (4.8%)

*CHT= chronic hypertension, SPE=superimposed pre-eclampsia *denotes outcomes that are significantly different between the compared groups **Severe hypertension= systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg*

The women who developed SPE had higher peak SBP and DBP (180 mmHg versus 160 mmHg; p=0.0003 and 107 versus 97 mmHg; p=0.004 respectively) and were more likely to require an emergency Caesarean section for delivery (76% versus 39%; p=0.006). Women with SPE were delivered earlier (median 33 weeks' gestation) compared to those without (median 39 weeks' gestation; p=<0.0001). with lower birthweight babies (1560g versus 3030g;) p=<0.0001) and a greater proportion of infants who required admission to the neonatal unit (76% versus 10%; p=<0.0001).

Table 7.3 Neonatal outcomes for the live births within the cohort

Outcome	All CHT n=94	SPE n=17	CHT no SPE n=77	Black ethnicity n=54	Non-Black ethnicity n=40
Birthweight, g Median (IQR)	2940 (2580 to 3260)	1560* (1040 to 2510)	3030 (2790 to 3460)	2980 (2520 to 3190)	2930 (2650 to 3530)
Birthweight <10th centile (SGA10) number (%)	29 (30%)	12* (71%)	17 (22%)	18 (33%)	11 (28%)
Birthweight <3rd centile number (%)	14 (14%)	10* (59%)	4 (5.2%)	9 (17%)	5 (13%)
Neonatal unit admission number (%)	21 (22%)	13* (76%)	8 (10%)	10 (19%)	11 (28%)

CHT= chronic hypertension, SPE=superimposed pre-eclampsia, SGA10= birthweight <10th centile
**denotes outcomes that are significantly different between the compared groups*

Analysis A: Comparison of vascular function parameters between women with chronic hypertension who did and did not develop superimposed pre-eclampsia

A summary of the comparison of vascular function parameters in women who did and did not develop SPE is in Table 7.4. Across gestation the SBP and DBP measurements taken by the Arteriograph® were higher in the women whose pregnancies were complicated by SPE (148 mmHg versus 139 mmHg; p=0.002 and 87 mmHg versus 82 mmHg; p=0.01), as were the central aortic pressure and the AIX adjusted for a heart rate of 75 beats per minute (139 mmHg versus 128 mmHg; p=0.001 and 29% versus 22%; p=0.01 respectively).

Table 7.4 Variation in vascular function parameters across gestation in women who did and did not develop superimposed pre-eclampsia

Parameter	SPE n=17 mean (SD)	CHT no SPE n=80 mean (SD)	Adjusted mean difference (95% confidence interval)	Significance (P value)
Brachial SBP (mmHg)	148 (17)	139 (15)	10 (4 to 16)	0.002
Brachial DBP (mmHg)	87 (10)	82 (10)	5 (1 to 9)	0.01
CAP (mmHg)	139 (22)	128 (16)	12 (5 to 20)	0.001
PWV (m/s)	9.0 (1.7)	8.6 (1.4)	0.6 (-0.2 to 1.3)	0.12
AIX (%)	21 (16)	17 (13)	4 (-1 to 9)	0.11
AIX-75 (%)	29 (13)	22 (12)	6 (1 to 11)	0.01

Mean difference adjusted for gestation. SD= standard deviation, SPE= superimposed pre-eclampsia, CHT= chronic hypertensive, SBP= systolic blood pressure, DBP= diastolic blood pressure, CAP= central aortic pressure, PWV= pulse wave velocity, AIX= augmentation index, AIX-75= augmentation index adjusted for a heart rate of 75 beats per minute

Analysis B: Comparison of vascular function parameters between women with chronic hypertension who delivered a small for gestational age infant (birthweight <10th centile) and those who delivered an infant with a birthweight ≥10th centile.

A summary of the comparison of vascular function parameters in women who gave birth to an SGA10 infant with those who gave birth to an infant with a birthweight above the 10th centile is presented in Table 7.5. Brachial SBP and DBP were significantly higher across gestation in the women who delivered an SGA10 infant (146 mmHg versus 138 mmHg; p=0.001 and 86 mmHg versus 82 mmHg; p=0.01 respectively). Mean central aortic pressure across gestation was 137 mmHg in women who gave birth to an SGA10 infant compared to 127 mmHg in women whose infant's birthweight was ≥10th centile (p=<0.0001). In addition, the mean PWV across gestation was 9.1 m/s in women who delivered an SGA10 infant compared to 8.5 m/s in those who did not (p=0.02).

Table 7.5 Variation in vascular function parameters across gestation in women who gave birth to a small for gestational age infant (<10th birthweight centile)

Parameter	SGA10 n=29 mean (SD)	CHT no SGA10 n=68 mean (SD)	Adjusted mean difference (95% confidence interval)	Significance (P value)
Brachial SBP (mmHg)	146 (18)	138 (13)	9 (4 to 14)	0.001
Brachial DBP (mmHg)	86 (13)	82 (9)	4 (1 to 8)	0.01
CAP (mmHg)	137 (22)	127 (15)	11 (5 to 18)	<0.0001
PWV (m/s)	9.1 (1.7)	8.5 (1.3)	0.7 (0.1 to 1.4)	0.02
AIX (%)	19 (15)	17 (13)	3 (-2 to 7)	0.25
AIX-75 (%)	26 (13)	22 (12)	4 (0 to 8)	0.05

Mean difference adjusted for gestation. SD= standard deviation, SGA10= birthweight <10th centile, CHT= chronic hypertensive, SBP= systolic blood pressure, DBP= diastolic blood pressure, CAP= central aortic pressure, PWV= pulse wave velocity, AIX= augmentation index, AIX-75= augmentation index adjusted for a heart rate of 75 beats per minute

Analysis C: Comparison of vascular function parameters between women with chronic hypertension of Black ethnicity and non-Black ethnicity

Table 7.6 summarises the vascular function comparisons made between women of Black and non-Black ethnicity with chronic hypertension in pregnancy. No significant differences in vascular function across gestation were found by ethnic group.

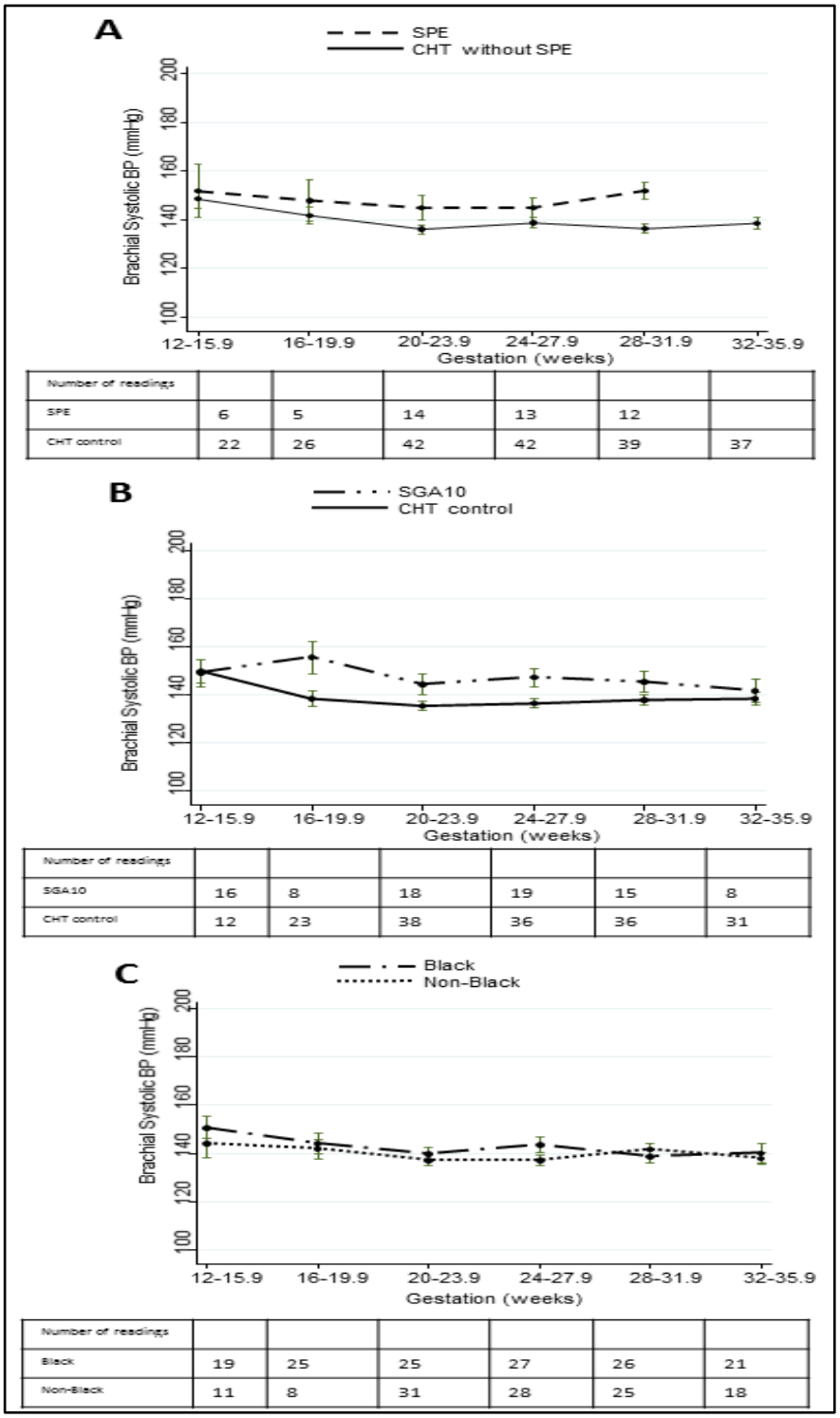
Table 7.6 Variation in vascular function parameters across gestation in women of Black and non-Black ethnicity

Parameter	Black n=55 mean (SD)	Non-Black n=42 mean (SD)	Adjusted mean difference (95% confidence interval)	Significance (P value)
Brachial SBP (mmHg)	142 (17)	139 (13)	4 (-1 to 8)	0.17
Brachial DBP (mmHg)	84 (11)	82 (9)	2 (-1 to 5)	0.18
CAP (mmHg)	132 (19)	128 (17)	5 (-1 to 11)	0.12
PWV (m/s)	8.7 (1.5)	8.6 (1.5)	0.3 (-0.3 to 0.9)	0.34
AIX (%)	18 (13)	17 (15)	2 (-2 to 6)	0.45
AIX-75 (%)	23 (12)	23 (14)	1 (-3 to 5)	0.52

Mean difference adjusted for gestation. SD= standard deviation, CHT= chronic hypertensive, SBP= systolic blood pressure, DBP= diastolic blood pressure, CAP= central aortic pressure, PWV= pulse wave velocity, AIX= augmentation index, AIX-75= augmentation index adjusted for a heart rate of 75 beats per minute

Longitudinal variation in vascular function parameters across gestation

The graphs in Figures 7.2 to 7.7 demonstrate the gestational variation in each vascular function parameter for each comparison (A, B and C).



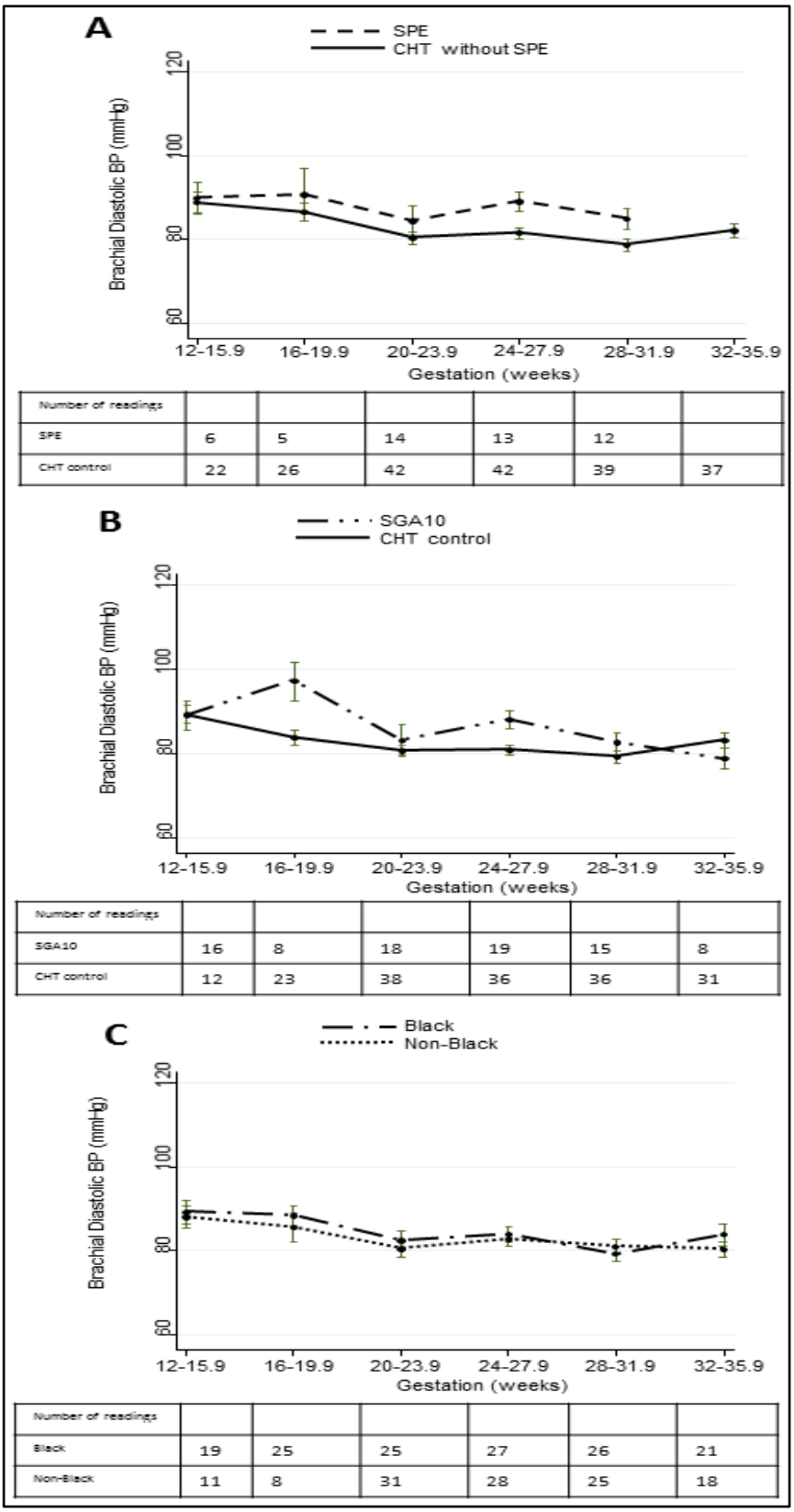
Number of readings						
SPE	6	5	14	13	12	
CHT control	22	26	42	42	39	37

Number of readings						
SGA10	16	8	18	19	15	8
CHT control	12	23	38	36	36	31

Number of readings						
Black	19	25	25	27	26	21
Non-Black	11	8	31	28	25	18

Figure 7.2 Brachial systolic blood pressure across gestation in pregnant women with chronic hypertension.

Comparison A: SPE versus no SPE. Comparison B: SGA10 versus no SGA10. Comparison C: women of Black ethnicity versus women of non-Black ethnicity. The limits of the axes represent the maximum and minimum value within the dataset for each parameter.



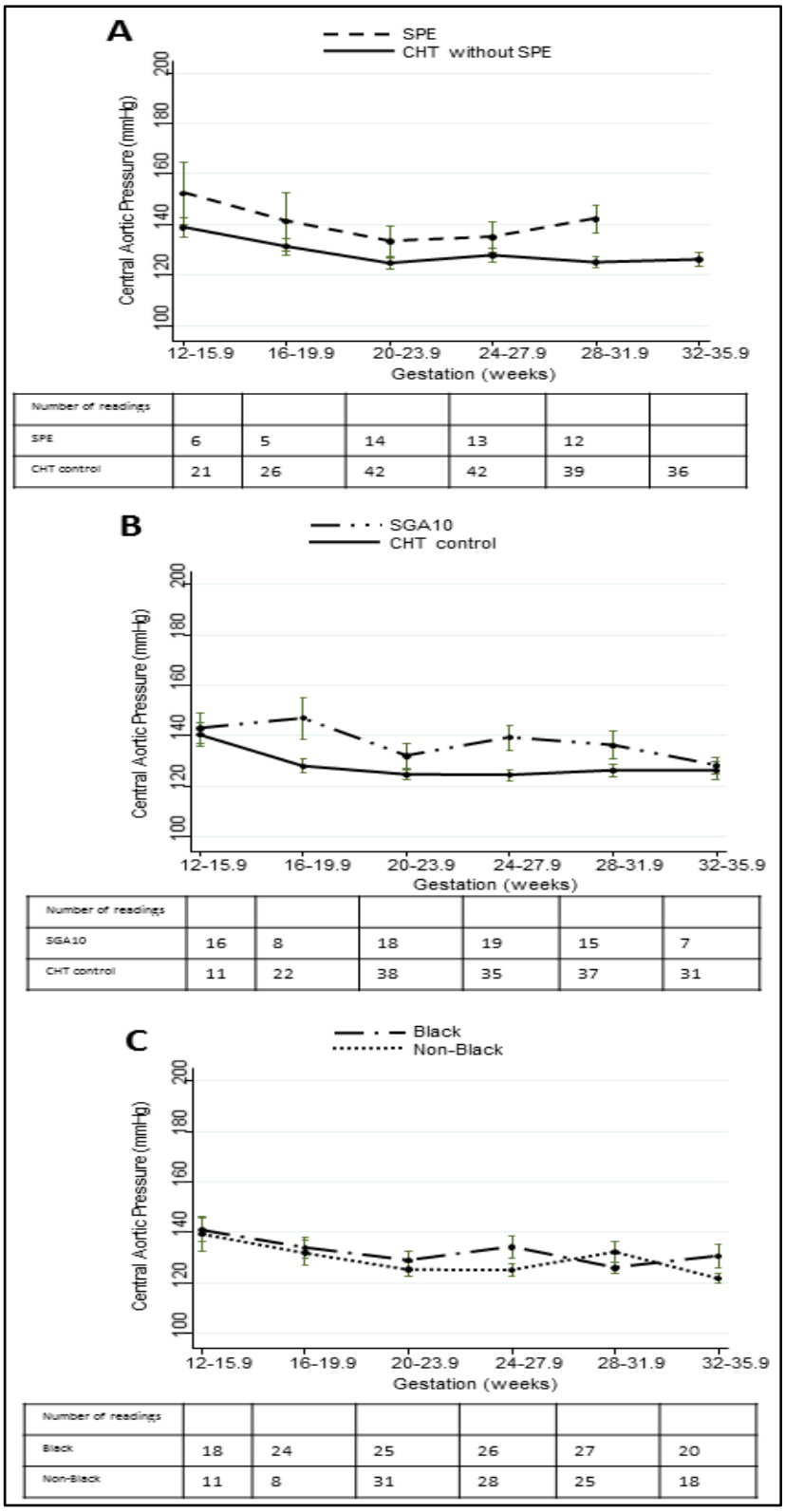
Number of readings						
SPE	6	5	14	13	12	
CHT control	22	26	42	42	39	37

Number of readings						
SGA10	16	8	18	19	15	8
CHT control	12	23	38	36	36	31

Number of readings						
Black	19	25	25	27	26	21
Non-Black	11	8	31	28	25	18

Figure 7.3 Brachial diastolic blood pressure across gestation in pregnant women with chronic hypertension.

Comparison A: SPE versus no SPE. Comparison B: SGA10 versus no SGA10. Comparison C: women of Black ethnicity versus women of non-Black ethnicity. The limits of the axes represent the maximum and minimum value within the dataset for each parameter.



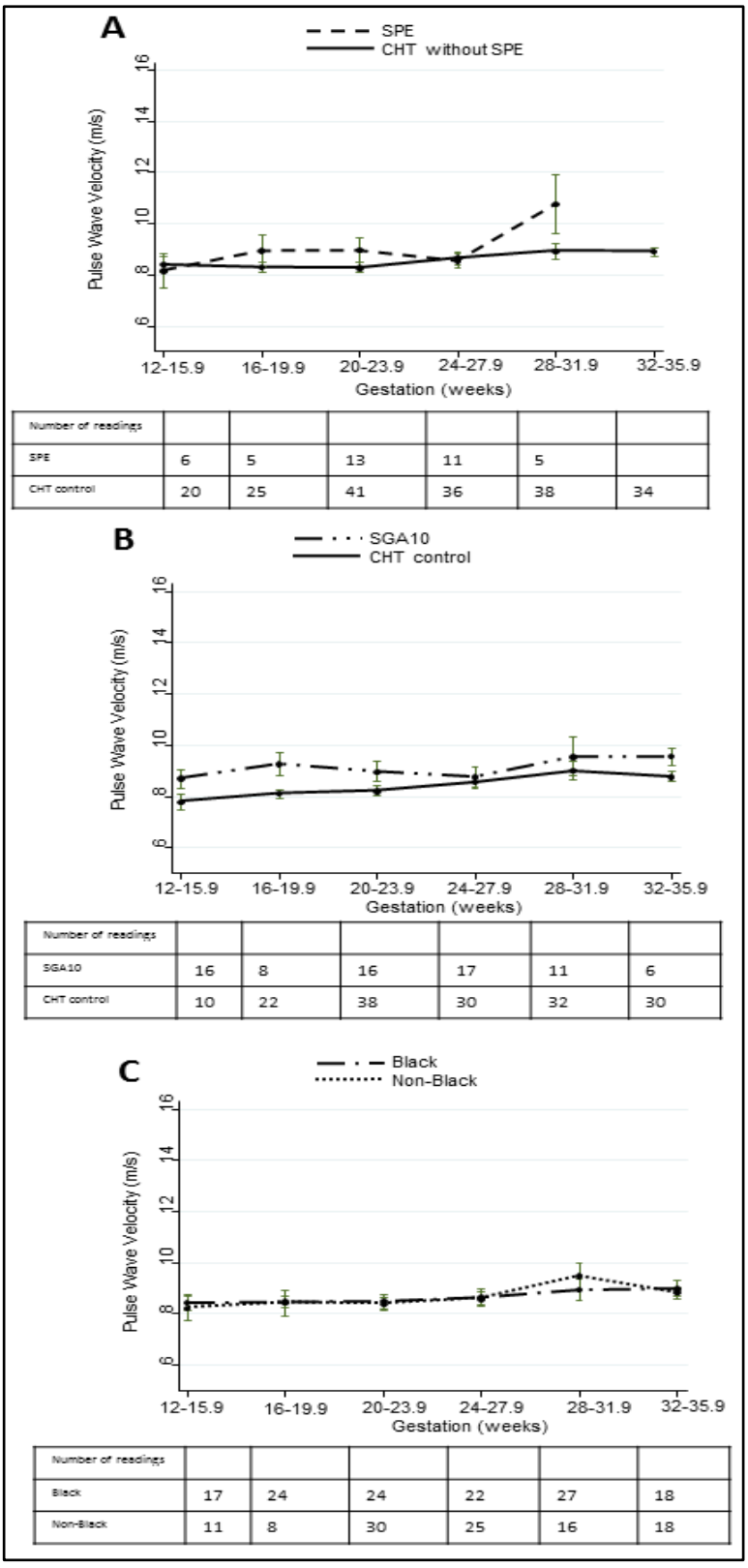
Number of readings						
SPE	6	5	14	13	12	
CHT control	21	26	42	42	39	36

Number of readings						
SGA10	16	8	18	19	15	7
CHT control	11	22	38	35	37	31

Number of readings						
Black	18	24	25	26	27	20
Non-Black	11	8	31	28	25	18

Figure 7.4 Central aortic blood pressure across gestation in pregnant women with chronic hypertension

Comparison A: SPE versus no SPE. Comparison B: SGA10 versus no SGA10. Comparison C: women of Black ethnicity versus women of non-Black ethnicity. The limits of the axes represent the maximum and minimum value within the dataset for each parameter.



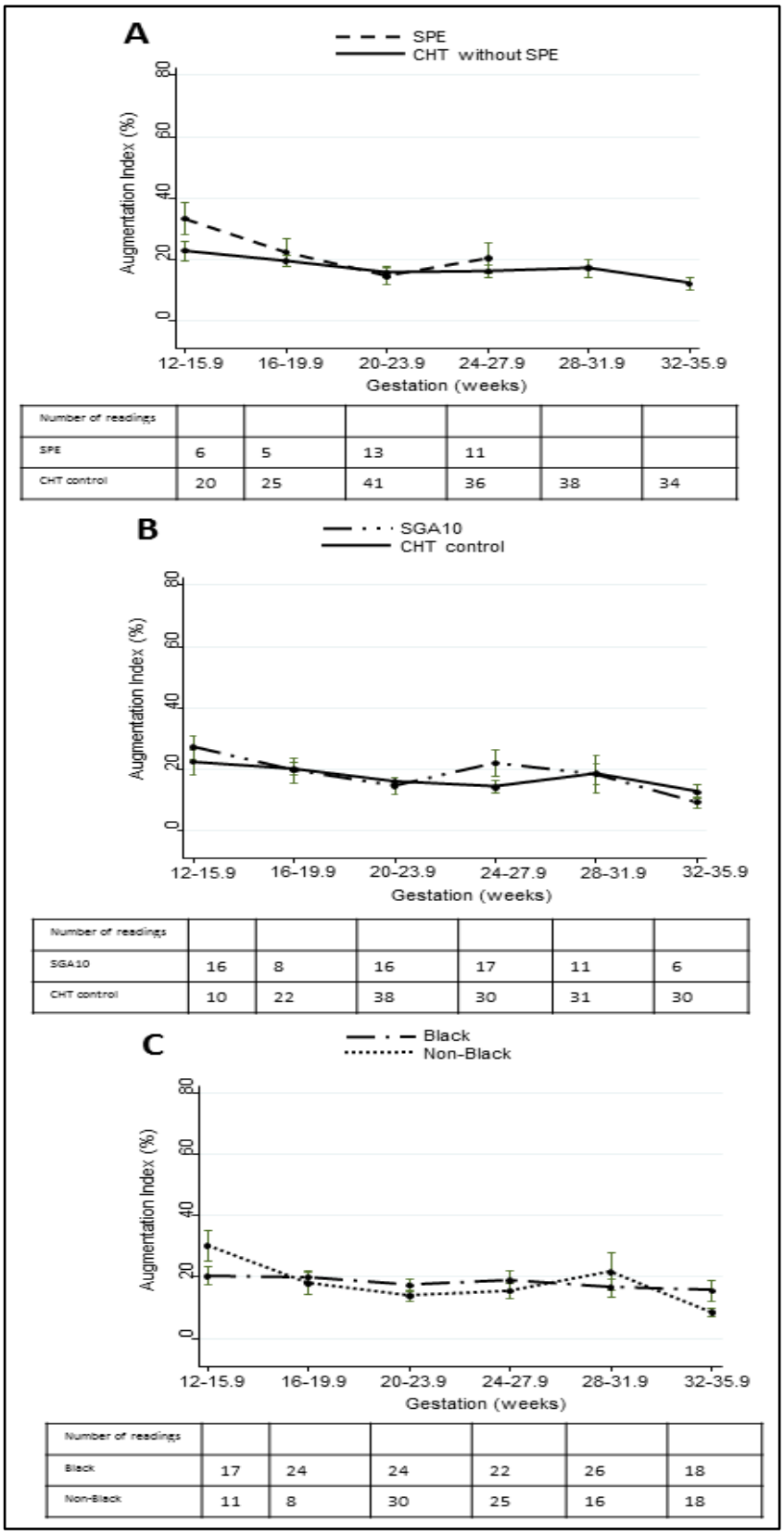
Number of readings						
SPE	6	5	13	11	5	
CHT control	20	25	41	36	38	34

Number of readings						
SGA10	16	8	16	17	11	6
CHT control	10	22	38	30	32	30

Number of readings						
Black	17	24	24	22	27	18
Non-Black	11	8	30	25	16	18

Figure 7.5 Pulse wave velocity across gestation in pregnant women with chronic hypertension

Comparison A: SPE versus no SPE. Comparison B: SGA10 versus no SGA10. Comparison C: women of Black ethnicity versus women of non-Black ethnicity. The limits of the axes represent the maximum and minimum value within the dataset for each parameter.



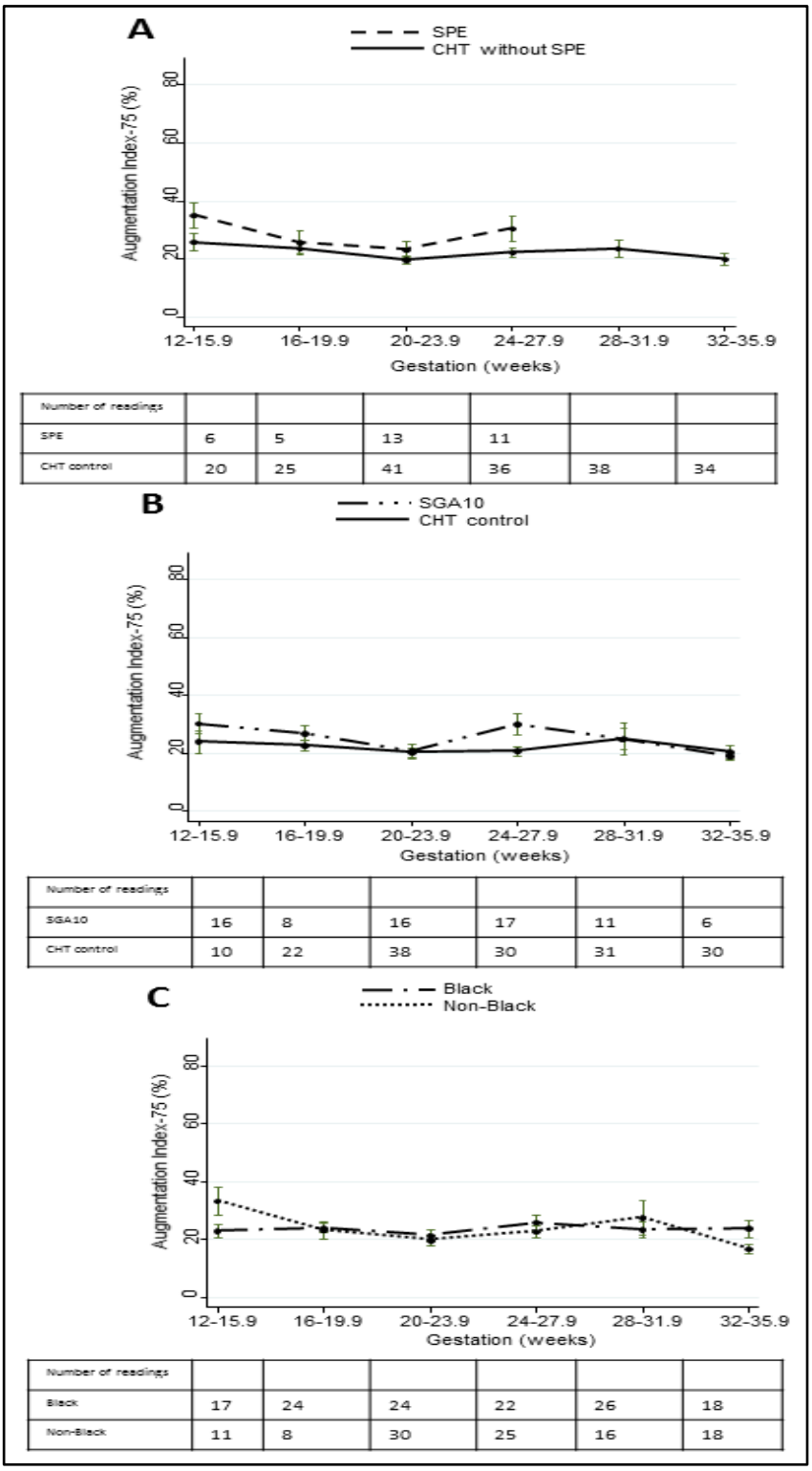
Number of readings						
SPE	6	5	13	11		
CHT control	20	25	41	36	38	34

Number of readings						
SGA10	16	8	16	17	11	6
CHT control	10	22	38	30	31	30

Number of readings						
Black	17	24	24	22	26	18
Non-Black	11	8	30	25	16	18

Figure 7.6 Augmentation index across gestation in pregnant women with chronic hypertension

Comparison A: SPE versus no SPE. Comparison B: SGA10 versus no SGA10. Comparison C: women of Black ethnicity versus women of non-Black ethnicity. The limits of the axes represent the maximum and minimum value within the dataset for each parameter.



Number of readings						
SPE	6	5	13	11		
CHT control	20	25	41	36	38	34

Number of readings						
SGA10	16	8	16	17	11	6
CHT control	10	22	38	30	31	30

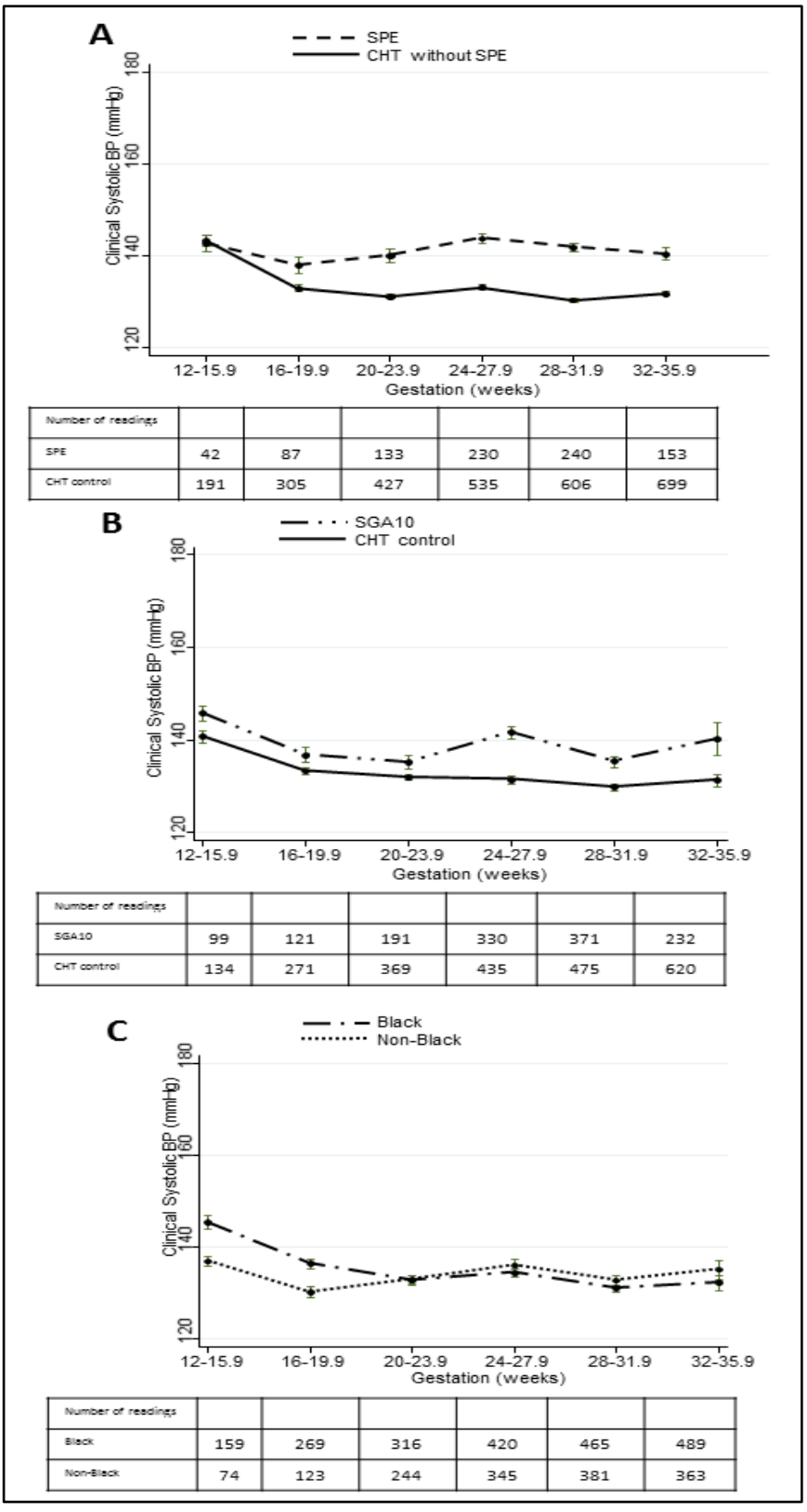
Number of readings						
Black	17	24	24	22	26	18
Non-Black	11	8	30	25	16	18

Figure 7.7 Augmentation index adjusted to a heart rate of 75 beats per minute across gestation in pregnant women with chronic hypertension

Comparison A: SPE versus no SPE. Comparison B: SGA10 versus no SGA10. Comparison C: women of Black ethnicity versus women of non-Black ethnicity. The limits of the axes represent the maximum and minimum value within the dataset for each parameter.

Comparison of clinical systolic and diastolic blood pressure readings for each comparison

Given the relationship observed between brachial SBP and DBP and outcomes as measured using the Arteriograph®, further comparison was made repeating analysis A, B and C utilising the clinically recorded blood pressure measurements taken within the study. This analysis confirmed that there was a significant relationship between brachial blood pressure and subsequent SPE with systolic blood pressure 11 mmHg higher across gestation (95% confidence interval 7 to 15 mmHg; p <0.0001) and diastolic blood pressure 5 mmHg higher across gestation (95% confidence interval 2 to 8 mmHg; p 0.003) in women who developed SPE compared to those who did not. Raised brachial blood pressure was also associated with subsequent SGA10 in women with chronic hypertension, with systolic blood pressure 9 mmHg higher (95% confidence interval 5 to 12 mmHg; p <0.0001) and diastolic blood pressure 4 mmHg higher (95% confidence interval 1 to 6 mmHg; p 0.002) in women who gave birth to SGA10 infants compared to women who gave birth to infants who had a birthweight ≥10th centile. No relationship was demonstrated between clinical blood pressure and ethnicity. Figures 7.8 and 7.9 present the comparisons made of clinical systolic and diastolic blood pressure measurements across gestation respectively.



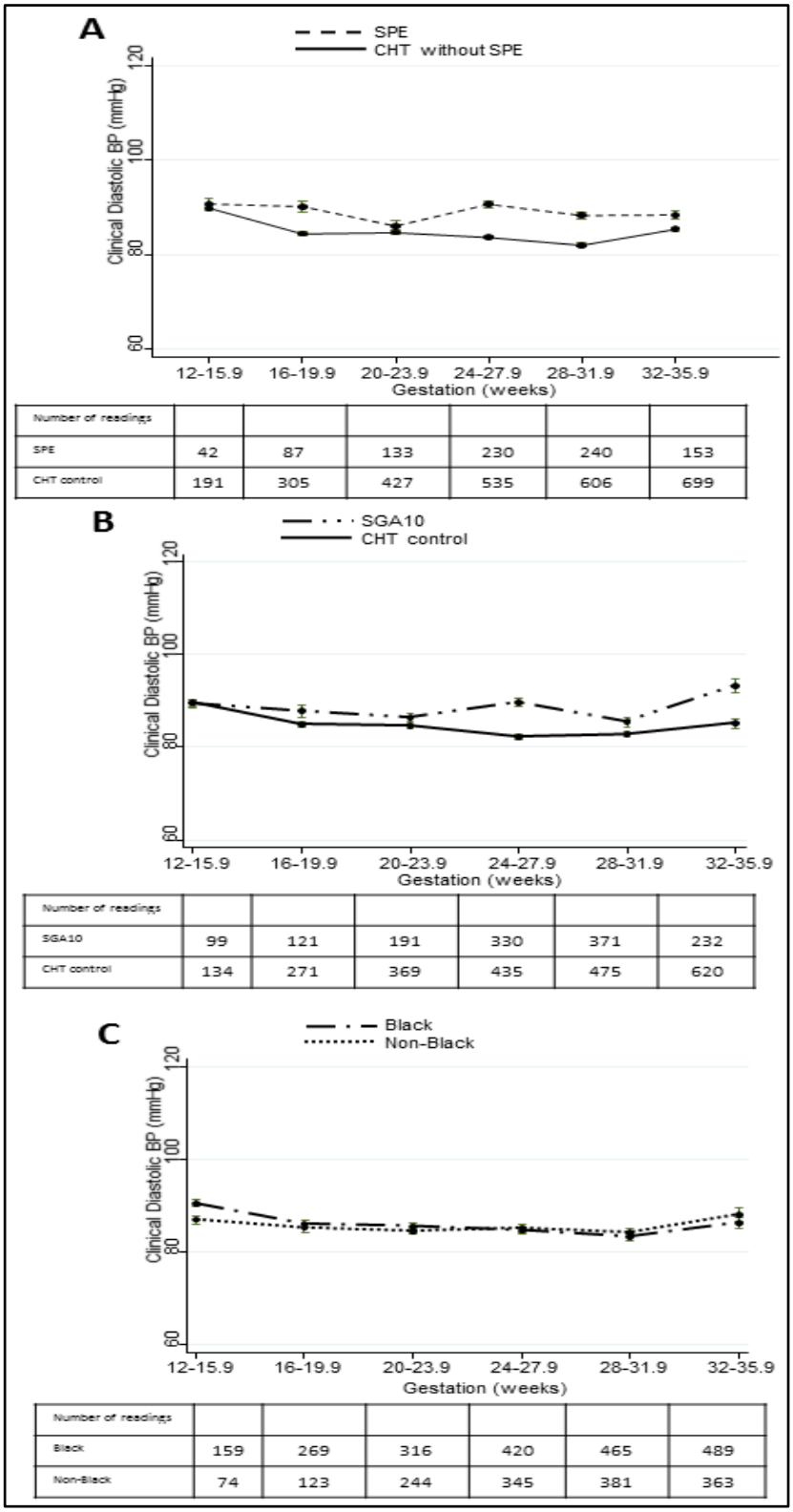
Number of readings						
SPE	42	87	133	230	240	153
CHT control	191	305	427	535	606	699

Number of readings						
SGA10	99	121	191	330	371	232
CHT control	134	271	369	435	475	620

Number of readings						
Black	159	269	316	420	465	489
Non-Black	74	123	244	345	381	363

Figure 7.8 Clinical systolic blood pressure across gestation in pregnant women with chronic hypertension.

Comparison A: superimposed pre-eclampsia (SPE) versus no SPE. Comparison B: Women giving birth to infants <10th birthweight centile. Comparison C: women of Black ethnicity versus non-Black ethnicity.



Number of readings						
SPE	42	87	133	230	240	153
CHT control	191	305	427	535	606	699

Number of readings						
SGA10	99	121	191	330	371	232
CHT control	134	271	369	435	475	620

Number of readings						
Black	159	269	316	420	465	489
Non-Black	74	123	244	345	381	363

Figure 7.9 Clinical diastolic blood pressure across gestation in pregnant women with chronic hypertension.

Comparison A: superimposed pre-eclampsia (SPE) versus no SPE. Comparison B: Women giving birth to infants <10th birthweight centile. Comparison C: women of Black ethnicity versus non-Black ethnicity.

7.5 Discussion

This cohort study demonstrates that longitudinally elevated brachial systolic and diastolic blood pressure predate the development of adverse pregnancy outcome in women with chronic hypertension. These findings are in keeping with data from other studies demonstrating an association between elevated blood pressure and adverse outcome.[133] An increase in other vascular function parameters across gestation also pre-dates the development of SPE and SGA10 in this cohort. Women with chronic hypertension are at high risk of adverse pregnancy outcome, as highlighted by this study. SPE was diagnosed in 18%, which is in keeping with the incidence reported in other studies of 17 to 25%.[7] Caesarean section was required for 63% of this cohort, which compares with 26% caesarean section rate in the general UK pregnant population (data obtained for NHS England maternity statistics 2013 to 2014).[324] Adverse perinatal outcomes were also increased with 24% of infants born before 37 weeks' gestation, 30% SGA10 and 22% of infants requiring neonatal unit admission.

To our knowledge this is the first study to report longitudinal changes in pulse wave analyses using the Arteriograph® device exclusively in women with chronic hypertension in pregnancy. An association between increased central aortic pressure and subsequent diagnosis of pre-eclampsia has previously been demonstrated by Khalil and colleagues (2014) using this device in women who were normotensive at study enrolment.[252] Additionally, raised AIX and AIX-75 have been demonstrated in women with pre-eclampsia, both prior to and at the time of diagnosis.[232,250-252] Our study did not demonstrate an association between unadjusted AIX and pregnancy outcome, but AIX-75 was increased across gestation in women who developed SPE, compared to those who did not. A cross-sectional cohort study of 41 pregnant women with chronic hypertension, conducted by Tomimatsu and colleagues (2014), also demonstrated an association between increased AIX-75 and SPE.[253] This study also demonstrated increased brachial SBP and CAP pre-dated the development of SPE with SGA10 at 26 to 32 weeks' gestation compared with women with chronic hypertension who had SPE alone, SGA10 alone, or no SPE/SGA10. The approach of subdividing their cohort did reduce the number of women within each group used for the comparative analysis and this reduction in power may have affected the results.

The relationship between blood pressure and placental insufficiency is complex. There are many studies that demonstrate an increased incidence of fetal growth restriction associated with chronic hypertension in pregnancy, both in association with and independently of a

diagnosis of SPE.[8,29,45,54] Previously fetal growth restriction has been linked to antihypertensive treatment in women with hypertensive disorders of pregnancy, with a hypothesis that the reduction in blood pressure caused by the antihypertensive agents also reduced placental blood flow, leading to fetal growth restriction.[129] However, the Control of Hypertension In Pregnancy Study (CHIPS, reported 2015) demonstrated that there was no adverse effect of tight blood pressure control (target DBP 80-85 mmHg), compared to less tight control (target DBP 100-105 mmHg), on the risk of SGA10 between intervention groups (16% versus 20%; odds ratio 0.78, 95% confidence interval 0.56 to 1.08).[15] The impact of antihypertensive treatment on the incidence of fetal growth restriction if a diastolic blood pressure target below 85 mmHg is utilised needs to be established, as the CHIPS protocol recommended cessation of antihypertensive treatment if diastolic was <80 mmHg. However, our study demonstrates an association between increased brachial SBP and DBP across gestation and subsequent delivery of an SGA10 infant in women with chronic hypertension in pregnancy. Though superimposed pre-eclampsia may explain some of this increased risk, the relationship between increased blood pressure and subsequent delivery of an SGA10 infant requires further investigation, as it seems probable that increased blood pressure increases the risk of placental insufficiency. The increase in PWV, a marker of arterial stiffness, associated with the subsequent birth of an SGA10 infant demonstrated by this study, would support this hypothesis.

There is evidence that pre-eclampsia is associated with subsequent increased cardiovascular risk. A systematic review reported by Bellamy and colleagues (2007), demonstrated that a diagnosis of pre-eclampsia in pregnancy was associated with a relative risk of 2.16 (95% confidence interval 1.86 to 2.52) for developing ischaemic heart disease after 11.7 years, and a relative risk for stroke of 1.81 (95% confidence interval 1.45 to 2.27) after 10.4 years compared to women whose pregnancies were not complicated by pre-eclampsia.[363] This study offers potential insight into the mechanisms of this increased risk, as arterial stiffness markers are increased in women who develop superimposed pre-eclampsia, compared to those who do not, and arterial stiffness parameters are increased in those with an increased cardiovascular risk in the non-pregnant population.[240,362]

No ethnic variation in vascular function parameters was demonstrated in this study. Khalil and colleagues (2009) also found no ethnic variation in vascular function parameters, but in normotensive pregnancy.[230] However, a study by Brewster and colleagues (2010) demonstrated increased resistance artery contractility in Black normotensive pregnant

women, compared with White.[367] In order to confirm if ethnic variation in vascular function parameters exist and have a role in the pathophysiology underpinning the ethnic disparity in pregnancy outcome observed in previous cohort studies, a much larger study is needed.

The strengths of this study include focusing on recruitment in women with chronic hypertension to allow investigation of vascular function differences in this group alone. The study was conducted at three centres, making the results more generalizable and including a wider-UK cohort. Performing longitudinal pulse wave analyses allowed assessment of changes in vascular function parameters that occurred prior to clinical diagnosis of any adverse outcome. The limitations include the relatively small number of participants, though our study was larger than previous studies that examined vascular function in chronic hypertension alone.[253] The potential clinical utility of these parameters in diagnosis of SPE could not be ascertained as no 'time of disease' readings were obtained, and 8.4% of readings did not record the AIX or PWV, suggesting further optimisation of this technique is required prior to establishing the use of this device in clinical practice.

Future research needs to establish whether the measurement of vascular function parameters in pregnancy complicated by chronic hypertension offers benefit above the standard brachial blood pressure measurements used in current clinical practice. This is particularly pertinent given the association demonstrated within this study between increased clinical systolic and diastolic blood pressure and subsequent SPE and/or SGA10. Differing antihypertensive agent effects on vascular function parameters have been observed, in the absence of brachial blood pressure variation.[244] If such treatment differences were observed in a pregnant population, the assessment of vascular function may prove a useful adjunct to current clinical management of chronic hypertension in pregnancy. It would also be beneficial to establish if vascular function parameters measured in the first or second trimester could be used to predict SPE or SGA10 and hence aid risk stratification and antenatal care pathways.

In conclusion, variation in vascular function parameters and brachial blood pressure exist longitudinally in pregnant women with chronic hypertension who develop adverse maternal and perinatal outcome. Further investigation of the potential clinical utility of these findings is warranted.

CHAPTER 8 CONCLUSIONS AND FUTURE RESEARCH

8.1 Summary of key findings

In this thesis I have demonstrated through a systematic review and meta-analysis that antihypertensive treatment substantially reduces the risk of severe hypertension in women with chronic hypertension in pregnancy compared to non-active treatment; no significant differences in other maternal or perinatal outcomes were observed with antihypertensive use. This systematic review highlights the paucity of data available to guide the treatment of chronic hypertension in pregnancy. Given the recent evidence that tight control of hypertension, compared with less tight control, in pregnancy reduces the risk of severe hypertension with no significant adverse perinatal outcome, the optimal antihypertensive agent(s) to achieve and maintain tight blood pressure control needs to be identified.

My cohort study of 4481 women with chronic hypertension in pregnancy confirmed, in a contemporary UK population, the increased risk of adverse maternal and perinatal outcomes compared with the general pregnant population. I demonstrated that Black ethnicity, compared to White, was the maternal characteristic most strongly associated with an increased risk of all adverse perinatal outcomes. This study included adjustment for deprivation and was conducted in a free healthcare setting suggesting that the impact of variation in outcome by ethnicity is likely to be mediated through multifactorial pathways, with potential pathophysiological differences that require further exploration.

As part of a wider team, I conducted the first randomised controlled feasibility trial comparing labetalol and nifedipine for treatment of chronic hypertension in pregnancy. The feasibility of conducting this study in pregnancy was confirmed, with 114 women randomised at four UK sites and 112 women completing the study. Labetalol and nifedipine demonstrate comparable effectiveness within the limits of this feasibility study, but much larger head-to-head randomised controlled trials are needed to establish which agent(s) provides optimal blood pressure reduction, potentially improving maternal outcome without causing perinatal harm. Mechanistic differences in treatment effect were demonstrated with a reduction in central aortic pressure, and not brachial blood pressure, across gestation in women randomised to nifedipine compared to labetalol. An increase in protein: creatinine ratio in women randomised to nifedipine, compared to labetalol, was also noted, but mean concentrations did not reach a threshold deemed clinically significant, so the importance of this finding is uncertain. This study also explored possible ethnic variation in drug response and

demonstrated a modest reduction in mean diastolic blood pressure across gestation in women of non-Black ethnicity (all ethnicities other from African and Caribbean). Outside pregnancy there is evidence that individuals of African and Caribbean family origin respond optimally to calcium-channel blockers rather than beta-blockers and the impact of ethnicity on choice of antihypertensive agent within pregnancy should be investigated further in a much larger study.

Further exploration of placental, endothelial and renal biomarkers in women with chronic hypertension in pregnancy demonstrated a strong association between low placental growth factor concentrations across gestation and subsequent development of superimposed pre-eclampsia and/or delivery of infants <3rd birthweight centile. The predictive performance of placental growth factor <100 pg/ml when measured at 20 to 23^{+6} weeks' gestation for fetal growth restriction (birthweight <3rd centile) was good and the potential clinical utility of this test to guide antenatal ultrasound surveillance in this high-risk group should be examined further. In addition, ethnic differences in the maternal systemic renin-angiotensin-aldosterone system were demonstrated with Black women with chronic hypertension having lower circulating renin and aldosterone concentrations across gestation compared with non-Black women. Interestingly renin and aldosterone concentrations decreased significantly in all ethnic groups postpartum suggesting the systemic renin-angiotensin-aldosterone system is upregulated during pregnancy in all women. No ethnic differences in the intrarenal renin-angiotensin system were demonstrated and given the complexity and number of components of the systemic renin-angiotensin-aldosterone system, the importance of ethnic variation in circulating maternal renin and aldosterone concentrations requires further investigation.

Vascular function assessment through pulse wave analysis and estimation of arterial stiffness indices shows promise for clinical utility in the general non-pregnant population. My study, examining variation in vascular function parameters across gestation in women with chronic hypertension in pregnancy, demonstrated increased arterial stiffness indices in women who had subsequent adverse outcome (superimposed pre-eclampsia and infant birthweight <10th centile), but also demonstrated a strong association between raised brachial systolic and diastolic blood pressure and subsequent adverse pregnancy outcome, making the additional clinical benefit of pulse wave analyses unclear in women with chronic hypertension in pregnancy.

8.2 Strengths and limitations

The strengths of the systematic review in Chapter 3 include that it is the largest examining the optimal antihypertensive treatment for chronic hypertension in pregnancy. The review also focused on chronic hypertension rather than a mixed group including women with gestational hypertension, which is important given the differing pathophysiology of these conditions. The systematic review is limited by the number of studies and the number of participants, but this highlights the paucity of data in this area and the need for further large randomised controlled trials addressing the optimal treatment of chronic hypertension in pregnancy.

To my knowledge, the cohort study is the largest UK dataset of women with chronic hypertension in pregnancy. Data was collated from three centres, which adds an additional strength and allows robust regression modelling to highlight maternal characteristics that are associated with an increased risk of adverse perinatal outcome in women with chronic hypertension. The study is limited by the absence of information about severity of hypertension during each pregnancy. Additionally, comparison of the cohort of women with chronic hypertension with the other women who had pregnancies during the study timeframe at each centre would have made a more robust comparison of the increased risk of each adverse outcome.

The randomised controlled feasibility study is, to my knowledge, the first to compare labetalol and nifedipine for control of chronic hypertension in pregnancy. Invaluable feasibility information was obtained to inform the design of the definitive trial. In addition, mechanistic differences in each antihypertensive treatment were found that warrant further exploration. Given this is a feasibility study, the clinical findings require validation in a much larger study.

The mechanistic sub-studies highlighted variation in biomarker and vascular function parameters that may provide insight into pathophysiological pathways increasing the risk of adverse maternal and perinatal outcome in women with chronic hypertension in pregnancy. They were small in size and require further investigation in larger cohorts and expansion of the parameters examined to further enhance our understanding.

8.3 Future research and perspectives

Chronic hypertension contributes significantly to global morbidity and mortality. The significant increase in adverse maternal and perinatal outcomes such as superimposed pre-eclampsia and fetal growth restriction in pregnancy complicated by chronic hypertension has again been highlighted in this body of work. Further research into the pathophysiology underpinning these increased risks in women with chronic hypertension in pregnancy warrants further investigation. In particular, the impact of ethnicity on pathophysiological mechanisms needs to be explored further, given the disparity in pregnancy outcomes.

This study has demonstrated that increased brachial blood pressure is associated with placental dysfunction in women with chronic hypertension and future research should assess if a more assertive approach to reducing blood pressure in the first and second trimester confers any improvement in pregnancy outcome. It is imperative that further randomised controlled trials in women with chronic hypertension in pregnancy examine the optimal antihypertensive agent(s) to achieve and maintain this reduction in blood pressure. In order to inform the design of the definitive trial, I undertook a national clinician survey assessing which antihypertensive agents are most commonly used as first-line treatment for chronic hypertension in pregnancy. This confirmed that labetalol is most commonly prescribed (84%, n=51), with nifedipine (30%, n=18) and methyldopa (24%, n=14) as other first-line agents (further details of findings in Appendix). I have also established a local Hypertension in Pregnancy Participant and Public Involvement group to ensure that the research questions considered in the definitive study are important to the women we care for and that outcomes included are patient centred.

The challenges of antihypertensive medication adherence in pregnancy need to be explored, as pregnant women are often faced with balancing home and work-life whilst managing their chronic condition, and the first-line antihypertensive agents in current use are taken at a minimum twice per day and often three times per day. Our group is examining the utility of urinary drug metabolites testing in samples taken from the women who participated in our randomised controlled feasibility trial to explore objective adherence and how this could be incorporated into the definitive trial. Other more subjective methods for monitoring adherence include the use of the Morisky scale. Consideration of the benefit of alternative antihypertensive agents such as amlodipine in pregnancy should also be made. Additional qualitative work should examine women’s experience of taking antihypertensive treatment during pregnancy and factors that could improve adherence.

Optimisation of the management of hypertension in pregnancy should be explored further with investigation of the use of home blood-pressure monitoring, offering women empowerment in the management of their chronic condition, that may benefit their future health. Other interventions and aspects of pre-pregnancy, antenatal and postpartum management need to be considered, such as dedicated antenatal clinics. The CHIPS trial has demonstrated that targeting a diastolic blood pressure of 85 mmHg in pregnancy reduces the risk of severe hypertension in women with hypertension, but it is unclear if further maternal benefit or perinatal harm would be associated with even tighter control. The SPRINT trial had to end recruitment early when a significant reduction in cardiovascular morbidity and mortality was demonstrated with a systolic blood pressure target of 120 mmHg compared to 140 mmHg (albeit with increased serious adverse events), and the potential impact of suboptimal control of hypertension in pregnancy on a woman's long-term health needs to be considered further, but carefully balanced with fetal and infant wellbeing.

Pregnancy offers a unique opportunity to educate and empower women about their chronic conditions and the potential impact on their future health. Chronic hypertension is the most common pre-existing medical condition associated with adverse maternal and perinatal outcomes and is additionally associated with long-term maternal morbidity and mortality. Given the increasing incidence of chronic hypertension with rising maternal age and the growing prevalence of obesity, further research is required to optimise the short and long-term health of these women and their babies.

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APPENDICES

Appendix 1 Prospero registration of systematic review

PROSPERO International prospective register of systematic reviews

Systematic review of antihypertensive treatment in pregnancy complicated by chronic hypertension

Louise Webster, Frances Conti-Ramsden, Paul Seed, Catherine Nelson-Piercy, Lucy Chappell

Citation

Louise Webster, Frances Conti-Ramsden, Paul Seed, Catherine Nelson-Piercy, Lucy Chappell. Systematic review of antihypertensive treatment in pregnancy complicated by chronic hypertension. PROSPERO 2015:CRD42015020733

Available from

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015020733

Review question(s)

In women with chronic hypertension in pregnancy:

• Which anti-hypertensive treatment is associated with fewest episodes of severe hypertension in pregnancy?

• Does frequency of adverse maternal outcomes (e.g. pre-eclampsia, stroke, death) and mode of delivery vary by antihypertensive agent?

• Does frequency of fetal and neonatal adverse outcomes (e.g. growth restriction, preterm delivery, neonatal unit admission) vary by antihypertensive agent?

Searches

The following databases will be searched:

- MEDLINE (via OVID)

- EMBASE (via OVID)

- Cochrane Central Register of Controlled Trials (CENTRAL)

Databases will be searched from their earliest entries until 30th April 2015. No language restriction will be used in searches. Searches will be adapted to each database and details of each planned strategy are listed in the appendix.

In addition, any currently registered relevant clinical trials will be searched for via:

- Clinicaltrials.gov

- ISRCTN.com

Other grey literature will be sought by reviewing thesis titles from WorldCat Dissertations and Theses database.

Types of study to be included

Randomised Controlled Trials only

Condition or domain being studied

Chronic hypertension in pregnancy and antihypertensive treatment

Participants/ population

The population is pregnant women diagnosed with chronic hypertension prior to pregnancy or diagnosed up to 20 weeks' gestation. The definitions of chronic hypertension used by each study will be tabulated. Where chronic hypertension is not described the study will be excluded. Both primary and secondary chronic hypertension will be included. Studies with intention to treat chronic hypertension, regardless of level of hypertension at study entry, will also be included. Studies in which participants had gestational hypertension (GH) or chronic hypertension will only be included if the data for the chronic hypertension population are reported separately

Intervention(s), exposure(s)

Types of Intervention

• Any antihypertensive drug compared with alternative intervention (e.g. bed rest) or placebo

• One antihypertensive versus another antihypertensive drug

Eligibility criteria (Published and unpublished RCTs in any language will be assessed for eligibility)

• Pregnant women with chronic hypertension randomised to antihypertensive treatment arm and compared prospectively with at least one other treatment arm

• Definition of chronic hypertension reported

Exclusion criteria

• Any trial designs other than RCT.

• Studies not separating outcome data of participants with gestational or chronic hypertension

Comparator(s)/ control

Types of Intervention

• Any antihypertensive drug compared with alternative intervention (e.g. bed rest) or placebo

• One antihypertensive versus another antihypertensive drug

Eligibility criteria (Published and unpublished RCTs in any language will be assessed for eligibility)

• Pregnant women with chronic hypertension randomised to antihypertensive treatment arm and compared prospectively with at least one other treatment arm

• Definition of chronic hypertension reported

Exclusion criteria

• Any trial designs other than RCT.

• Studies not separating outcome data of participants with gestational or chronic hypertension

Context

Chronic hypertension (CHT) is estimated to affect up to 2-3% of UK pregnancies. This figure is set to increase with an ageing maternal population and the rise in obesity. Pregnancies complicated by CHT are associated with an increased risk of adverse outcomes for mother and baby. It is unclear if outcomes can be altered through choice of antihypertensive agent.

Outcome(s)

Primary outcomes

• Maternal

- Severe hypertension (defined as SBP>160mmHg and/or DBP>110mmHg or as given in paper, with tabulated definitions)

• Fetal/Neonatal

- Birthweight

Secondary outcomes

• Maternal

- Superimposed pre-eclampsia (with tabulated definitions)

- Need for additional antihypertensive agent during pregnancy (enteral or parenteral)

- Caesarean section delivery

- Estimated blood loss at delivery

- Eclampsia

- HELLP syndrome (with tabulated definitions)

- Placental abruption

- Other severe maternal morbidity: Disseminated Intravascular Coagulation, Acute Kidney Injury, Acute Liver Injury, Stroke etc.

- Intensive Therapy Unit/High Dependency Unit admission nights

- Maternal death

- Adverse events and drug side effects, including numbers withdrawn from each trial and reasons why (if available)

• Fetal/Neonatal:

- Fetal loss: Miscarriage if <24 weeks' gestation, Stillbirth >24 weeks' gestation (or as defined)

- Neonatal Death (death within the first 28 days of life)

- Preterm birth (<37 weeks and subdivided into <34 weeks wherever possible)

- Small for gestational age (SGA) babies (subdivided into birth centiles <10th centile, <3rd centile where possible)

- APGAR score at 5 minutes

- Arterial cord pH

- Neonatal unit admission

- Any neonatal morbidity thought to be related to maternal antihypertensive treatment such as hypo/hypertension, hypoglycaemia, etc.

Data extraction, (selection and coding)

The titles and abstracts generated from the database searches will be independently screened by two authors. If either author considers the study to meet inclusion criteria it will be included for full text assessment. Any disagreements will be resolved by involving a third independent reviewer. Any foreign language trials will be translated. Data from eligible trials will be manually extracted and entered into a standard extraction table independently by the two primary reviewers. Data from all studies will then be collectively tabulated. Where there is lack of clarity in data or study design, every effort will be made to contact the authors of the RCT for further information.

Data will be collected and tabulated on:

- Definition of chronic hypertension

- Clinical outcomes of interest as defined

- Criteria specified by Risk of Bias Tool

- Funding source

Risk of bias (quality) assessment

Each individual RCT will be quality assessed by one author using the Cochrane Collaboration Risk of Bias tool and then checked by a second author. Where there are any disagreements, they will be resolved by discussion with a third author. The following areas of each study will be considered for bias:

• Sequence generation

• Allocation concealment

• Blinding of participants, personnel and outcome assessors

• Incomplete outcome data

• Selective outcome reporting

• Any other sources of bias (including funding source)

Sub-group analysis will be performed based on this quality assessment.

Strategy for data synthesis

The review will be performed in line with PRISMA guidelines. For all outcomes the analysis will be conducted on an intention to treat basis. If a study contains only per-protocol data for a particular endpoint, it will be excluded from the main analysis. Meta-analysis will be undertaken where there is more than one study with analysable data. When there is only one study, the estimates from that study will be presented. Treatment effects will be presented as estimated differences in the mean or odds ratios with 95% confidence intervals. In the event of important significant treatment effects, the Number Needed to Treat (NNT) or Number Needed to Harm (NNH) will also be given. Conventional significance will be at the usual 5% level (2-sided).

Heterogeneity of results between studies will be tested using a Chi2 test. Significant heterogeneity will be assessed using Tau2 and by visual inspection of the forest plot.

Where there are sufficient studies of different populations, entry criteria or treatments, meta-regression and subgroup analysis will be used to investigate the differences between study results. Meta-regression will be performed with reported variables that are suspected to influence efficacy of treatment. Publication bias will be investigated using Egger's test and funnel plots.

Where data collected are insufficient for quantitative synthesis, they will be tabulated for presentation and explored in the discussion. If outcomes of interest are not able to be quantitatively synthesised, recommendations for the definitive trial to obtain these data will be made in the study conclusions

Analysis of subgroups or subsets

Subgroup analysis will be performed by:

- Ethnicity

- Age

- BMI

- Quality

Dissemination plans:

It is intended that the results of this review will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

Contact details for further information:

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Organisational affiliation of the review King's College London (www.kcl.ac.uk)

Review team

Dr Louise Webster, King's College London

Dr Frances Conti-Ramsden, King's College London

Mr Paul Seed, King's College London

Professor Catherine Nelson-Piercy, King's College London

Dr Lucy Chappell, King's College London

Anticipated or actual start date	01 May 2015
Anticipated completion date	02 May 2016
Funding sources/sponsors	King's College London
Conflicts of interest	None known
Language	English
Country	England

Subject index terms status

Subject indexing assigned by CRD

Subject index terms: Antihypertensive Agents; Female; Humans; Hypertension; Pregnancy; Pregnancy Complications, Cardiovascular

Stage of review	Ongoing
Date of registration in PROSPERO	21 May 2015
Date of publication of this revision	21 May 2015

DOI 10.15124/CRD42015020733

Appendix 2 ISRCTN registration of randomised controlled feasibility study

http://www.isrctn.com/ISRCTN40973936?q=ISRCTN40973936&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10&searchType=basic-search

ISRCTN40973936 DOI 10.1186/ISRCTN40973936

Pregnancy And chronic hypertension; NifeDipine or labetalol as Anti-hypertensive treatment.

Condition category	Circulatory System
Date applied	08/07/2014
Date assigned	10/09/2014
Last edited	30/03/2016
Prospective/Retrospective	Retrospectively registered
Overall trial status	Completed
Recruitment status	No longer recruiting

Plain English Summary:

Background and study aims

Chronic hypertension is high blood pressure that usually needs to be treated with medication. It is important that high blood pressure is diagnosed and treated; without treatment it can cause damage to the heart, brain and kidneys, and complications such as a stroke. Around 3% of pregnant women have been diagnosed with high blood pressure before they become pregnant. A pre-existing high blood pressure puts pregnant women at an increased risk of complications in pregnancy such as pre-eclampsia and the baby not growing properly. We want to find out which one of two different drugs work best at lowering the blood pressure in pregnant women without any harmful effects for the mother or the baby. Both drugs are commonly used in pregnancy. Labetalol has a license for pregnancy which means that it has undergone clinical trials that have found it to be safe and effective for its use. Nifedipine is not licensed in pregnancy but can be used 'off-label' (outside its license) if it is felt that the benefits of treatment are likely to outweigh the risks of harm to the mother or baby. These medications have been used by doctors in the UK for many years to treat pregnant women with high blood pressure and the medicines safety watchdog has reviewed this study and given its approval. As the choice of drug for high blood pressure outside of pregnancy depends partly

on ethnic background, our study is also looking at which treatment works best in pregnant women from different ethnic backgrounds.

Who can participate?

Women aged 18 and over, with chronic hypertension, between 12 and 28 weeks pregnant with one baby, and who need treatment for their blood pressure.

What does the study involve?

We are comparing two of the main drug treatments for chronic hypertension in pregnancy: labetalol and nifedipine. Participants are randomly allocated into 1 of 2 groups. Those in group 1 are given labetalol. Those in group 2 are given nifedipine. Both participants and their doctors know which treatment they are getting to make sure they are taking the right dose. All participants are seen regularly by healthcare professionals and are asked to give extra blood and urine samples on five occasions during their pregnancy, usually at the same time that their routine blood tests are performed. These samples are used to measure substances in the blood and urine at the end of the study to see if we can find out how each drug works. Participants are also asked for extra measurements of their blood pressure and to have a simple ultrasound (at the base of the neck) to check how the different drugs are working.

What are the possible benefits and risks of participating?

We know that both treatments will lower a woman's blood pressure, which helps avoid complications of high blood pressure in pregnancy. Each participant is seen regularly by the hospital doctors and midwives (as usual) and by the research team. The PANDA trial will provide information to help improve the treatment of women with high blood pressure in pregnancy in the future. We do not anticipate any serious side-effects from either drug. Both of them are taken by lots of pregnant women worldwide and serious side-effects are rare. A woman cannot take labetalol if she suffers from asthma or some heart conditions. Possible side-effects do, however, include, feeling faint on standing, headache, rashes, scalp tingling, difficulty in passing urine, tummy pain, nausea, vomiting and liver damage. A woman cannot take nifedipine if she has certain heart conditions. Possible side-effects include nausea, vomiting or diarrhoea, swelling of the legs, palpitations, headache and dizziness.

Where is the study run from?

The lead centre for the trial is Guy's and St Thomas' Hospital, London. The maternity units in Manchester and Leicester are also taking part.

When is the study starting and how long is it expected to run for?

August 2014 to September 2015

Who is funding the study?

The study is being funded by Tommy's Charity and by the King's Health Partners Challenge Fund.

Who is the main contact?

Dr Lucy Chappell

Contact details

Women's Health Academic Centre, St Thomas' Hospital, London, SE1 7EH, United Kingdom

+44 (0)20 7188 3639

lucy.chappell@kcl.ac.uk

Additional identifiers

EudraCT number 2013-003144-23

Study information

Scientific title

Labetalol or nifedipine for treating chronic hypertension in pregnancy

Acronym

PANDA

Study hypothesis

Nifedipine is as effective as labetalol at controlling blood pressure in women with chronic hypertension in pregnancy, with greater efficacy in women of African/ Caribbean family origin

Ethics approval

1. East of England- Cambridge East Research Ethics Committee (REC), 03/02/2014, REC Ref 13/EE/0390

2. Medicines and Healthcare products Regulatory Agency (MHRA), 31/01/2014, Ref: 14523/0251/001-0002

Study design	Randomised controlled trial (feasibility study)
Primary study design	Interventional
Secondary study design	Randomised controlled trial
Trial setting	Hospitals
Trial type	Treatment

Patient information sheet

Not available in web format, please use the contact details below to request a patient information sheet

Condition Chronic hypertension in pregnancy

Intervention

Women with be randomised to one of two treatments: labetalol or nifedipine, with the dose adjusted for blood pressure control

Primary outcome measures

As of 24/02/2016:

1. Primary clinical outcome measure: Highest systolic blood pressure (BP) between randomisation and delivery (highest of any recorded systolic BP measurement made between gestation at randomisation and gestation at delivery, excluding recordings made on the day of delivery and in addition average systolic BP during each pregnancy between randomisation and delivery will be calculated (using all available systolic BPs taken clinically using area under the curve by trapezium method)

2. Primary process outcome measure: Number of women enrolled per site per month (calculated at end of trial as total number of women enrolled per site divided by number of months of enrolment at that site)

Previous

1. Primary clinical outcome measure: Highest systolic blood pressure between randomisation and delivery (highest of any recorded systolic blood pressure measurement made between gestation at randomisation and gestation at delivery, excluding recordings made in labour)

2. Primary process outcome measure: Number of women enrolled per site per month (calculated at end of trial as total number of women enrolled per site divided by number of months of enrolment at that site)

Secondary outcome measures

Clinical:

1. Maternal outcomes including:

1.1. Maternal morbidity or mortality (pre-eclampsia, eclampsia, intracranial haemorrhage or infarct, myocardial ischaemia/ infarction, intubation, pulmonary oedema, hepatic dysfunction, acute renal insufficiency, placental abruption, post-partum haemorrhage) (assessed on maternal discharge after delivery)

1.2. Gestation at delivery (assessed at delivery)

1.3. Mode of delivery (assessed at delivery)

1.4. Indication for delivery (assessed at delivery)

1.5. Number of episodes of systolic BP >=160mmHg, >=150mmHg (including home monitoring) (assessed between randomisation and delivery, excluding recordings made in labour)

1.6. Diastolic BP <80mmHg (assessed between randomisation and delivery, excluding recordings made in labour)

1.7. Need for additional oral or parenteral antihypertensive medication (assessed between randomisation and delivery)

2. Perinatal outcomes including:

2.1. Neonatal morbidity (admission to neonatal unit (length and place of stay), respiratory distress syndrome, need for ventilator support, intraventricular haemorrhage, confirmed infection, necrotising enterocolitis, seizures, encephalopathy, retinopathy of prematurity, other indications and main diagnoses related to neonatal unit admission) (assessed on discharge of infant)

2.2. Stillbirth (assessed at time of death)

2.3. Neonatal death (assessed at time of death)

2.4. Birth weight (assessed at delivery)

2.5. Birth weight centile (assessed at delivery)

2.6. Umbilical artery pH at birth (assessed at delivery)

3. Health resource use outcomes including:

3.1. Number of antenatal attendances (clinic and day unit) (assessed on maternal discharge)

3.2. Maternal admission nights (ward, delivery suite, intensive care) (assessed on maternal discharge)

3.3. Neonatal admission nights (including level of care) (assessed on discharge of infant)

4. Process:

4.1. Medication adherence (through self-report and pill count) (assessed as average of self-report and average of pill count checked at each visit between randomisation and delivery)

4.2. Side-effects of medication (assessed through direct questioning at each antenatal visit between randomisation and delivery)

4.3. Satisfaction with medication (assessed through postnatal questionnaire)

Overall trial start date	14/08/2014
Overall trial end date	31/05/2016

Eligibility

Participant inclusion criteria

1. Chronic hypertension (defined as diastolic BP >=90mmHg present at booking or before 20 weeks' gestation, or requiring treatment outside pregnancy and/or at time of referral)

2. Gestation 12-28 weeks at recruitment

3. Singleton pregnancy

4. Able to provide informed consent

5. Age >=18 years

Participant type	Patient
Age group	Adult
Gender	Female

Target number of participants 114

Participant exclusion criteria

1. Contraindication to labetalol (including asthma, uncontrolled heart failure, Prinzmetal's angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third- degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; phaeochromocytoma) or nifedipine (including cardiogenic shock; advanced aortic stenosis; within 1 month of myocardial infarction; unstable or acute attacks of angina)

2. Insufficient understanding of the trial

Recruitment start date 14/08/2014

Recruitment end date 30/09/2015

Trial participating centre

Women's Health Academic Centre, St Thomas' Hospital, London, SE1 7EH, United Kingdom

Sponsor information

Organisation

Kings College London, Guys and St Thomas's NHS Foundation Trust (UK)

Sponsor details

KHP-CTO, 16th Floor Tower Wing, Great Maze Pond, London, SE1 9RT, United Kingdom

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Sponsor type Hospital/treatment centre

Funders

Funder type Charity

Funder name Tommy's Charity and KHP Challenge Fund (UK)

Editorial Notes

30/03/2016: Ethics approval information added. 25/02/2016: changed overall trial end date from 30/09/2015 to 31/05/2016

Appendix 3 Clinician survey results

Tommy's
Registered charity no 1060508

ACTION ON PRE-ECLAMPSIA

KING'S HEALTH PARTNERS

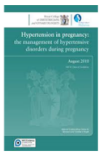
An Academic Health Sciences Centre for London
Women's Health Academic Centre

Pioneering better health for all

National variation in the management of chronic hypertension in pregnancy

LM Webster, C Nelson-Piercy, LC Chappell
Division of Women's Health, King's College London, Women's Health Academic Centre,
10th floor North Wing, St Thomas' Hospital, SE1 7EH

Introduction



- Chronic hypertension complicates 3% of pregnancies
- It is associated with adverse maternal and perinatal outcomes
- The NICE Hypertension in Pregnancy guideline does not recommend a first line antihypertensive treatment for chronic hypertension as evidence is sparse to guide optimal agent(s)
- Treatment target for hypertensive disorders in pregnancy of <150/100 mmHg is currently recommended, but given the recent findings of the Control of Hypertension in Pregnancy Study demonstrating reduction in severe maternal hypertension using a target diastolic blood pressure of ≤85 mmHg, changes in practice may be noted

CHIPS

Aim:

- To assess the national variation in prescribing patterns of antihypertensive agents and treatment targets used for chronic hypertension in pregnancy

Methods

MOMS
MACDONALD OBSTETRIC MEDICINE SOCIETY

SurveyMonkey

- A Survey Monkey was constructed to answer the stated aims and distributed via email to members of the MacDonald Obstetric Medicine Society and the London Obstetric Medicine Group
- Geographical regions were targeted to ensure answers were received from all areas of the UK
- Data was collated and presented as proportions

Results

- 62 clinicians responded to the questionnaire
- At least one response was received from a clinician practicing in each geographical region
- Consultants represented 79% (n=45) of those who answered, with the remaining responders trainees grade ST3-7
- Obstetricians accounted for 81% (n=46) of responders, with 16% (n= 9) obstetric physicians and 3% (n=2) general practitioners

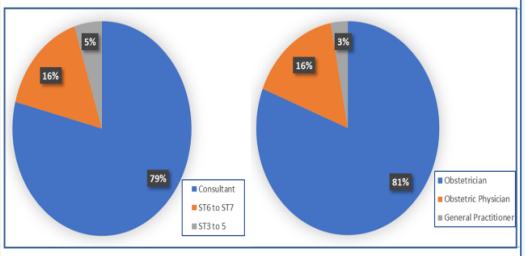


Figure 1: *Proportion of responses by grade of clinician and specialty*

Results continued

Table 1: *Prescribing patterns for first line antihypertensive treatment of chronic hypertension in pregnancy*

Antihypertensive agent	I would prescribe this treatment as first line for chronic hypertension in pregnancy	I would only prescribe this agent if there was a contraindication /adverse reaction to the other agent	I would only prescribe this agent as second or third line treatment	I would not prescribe this agent in pregnancy
Labetalol	51 (84%)	1 (2%)	9 (15%)	0
Nifedipine	18 (30%)	16 (27%)	26 (43%)	0
Methyldopa	14 (24%)	17 (29%)	28 (47%)	0

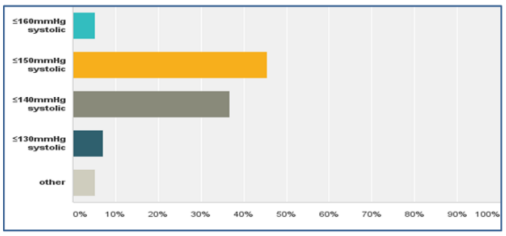


Figure 2: *Proportion of clinicians using each systolic blood pressure treatment target*

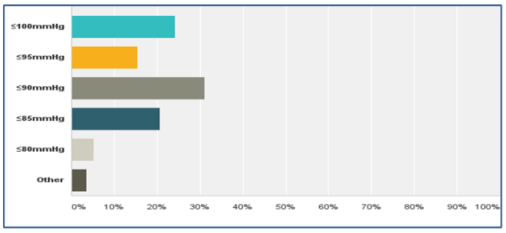


Figure 3: *Proportion of clinicians using each diastolic blood pressure treatment target*

- The following were rated as the most important outcomes of antihypertensive treatment in pregnancy complicated by chronic hypertension:
  - Reduction in incidence in episodes of severe hypertension 55% (n=31)
  - Reduction in hospital admission for complications such as severe hypertension 32% (n=18)
  - BP maintained throughout pregnancy within target range 29% (n=17)
- A dedicated antenatal clinic for the care of women with chronic hypertension was available in the hospitals of 57% (n=32) of those responding

Conclusions

- Variation in antihypertensive agent prescription and target therapeutic blood pressure for the treatment of chronic hypertension in pregnancy exists nationally
- Randomised controlled trials of the commonly used antihypertensive agents for the treatment of chronic hypertension in pregnancy are required to guide prescription
- Awareness of the evidence available to guide therapeutic treatment targets warrants further promotion

KING'S College LONDON

Guy's and St Thomas' Hospital NHS
NHS Trust

NHS
National Institute for Health Research